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C O R N E L L
U N I V E R S I T Y
M E D I C A L B U L L E T I N

VOLUME XII

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OCTOBER, 1922

STUDIES FROM THE
Department of
P H Y S I O L O G Y
VIII

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Cornell University Medical College

THE DEPARTMENT OF PHYSIOLOGY

GRAHAM LUSK

Professor of Physiology

DAYTON J. EDWARDS

Associate Professor of Physiology

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THE ARTERIAL PRESSURE CURVE AS INFLUENCED BY THE OCCLUSION OF CERTAIN VASCULAR AREAS AND BY HISTAMINE

D. J. EDWARDS

*From the Physiological Laboratory, Cornell University Medical College, New
York City*

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It has been shown in a number of researches by Wiggers (1) that the contour of the pressure curve recorded by the membrane manometer affords reliable qualitative data on the dynamics of the circulation. An outstanding feature of this method is that it gives information concerning the failure of normal dynamic relations earlier than the blood pressure results. It has made possible, therefore, a fairly precise designation of the onset of circulatory failure (2).

In the course of studies on blood flow (3) the use of a recording stromuhr made it necessary to close for periods of as much as twenty minutes the main blood vessels supplying visceral organs and in other instances those supplying the extremities. Roy and Brown (4) were probably the first to call attention to the fact that occlusion causes in the frog a dilatation of the arterioles to twice their normal size in two minutes, the effect extending also into the capillaries and veins. Recently attention has been directed to the possible harmful tendency of occlusion measures by the experiments of Mann (5) in which he shows that a shock-like condition can be produced by ligating all of the limb structures excepting the main artery, and Erlanger and Gasser (6) have shown that a similar condition results from a partial obstruction of the inferior cava for about a 2-hour period. In view of these results it is obviously desirable to know whether the less extreme measures used in blood flow experiments produce early changes in the dynamics, also whether there are differences in the character as well as the time of appearance, which distinguish obstructions of central areas from those involving peripheral organs.

There has been included in the program a study of the influence of histamine on the pressure curve, since the observed capillary toxicity of this product suggested a causal relation to the effects following occlusion of vascular areas.

SEGMENTAL ACTIVITY IN THE HEART OF THE LIMULUS

D. J. EDWARDS

From the Physiological Laboratory, Cornell University Medical College, New York City

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In the structural make-up of the *Limulus* heart the arrangement of the muscular elements into a long tube with well-defined segments, and the grouping of the nervous elements into a median ganglion and lateral nerves, are features which have a significant bearing upon its functional activity. Attention is especially directed to these features, since it appears from the work of Carlson (1) and others that activity in this heart is initiated and conditioned by this intrinsic nervous system, and that contraction in all segments is practically simultaneous. These considerations have suggested the present study, which is an analysis of the contractile process in the different parts of the muscular tube, and of the sequence of activity in the different segments in an attempt to discover the exact temporal relations of the different parts.

In order to make a detailed study of the contraction event it is necessary to employ instruments of unquestionable efficiency. The shortcomings of the suspension method of recording heart action are too well known to need repeating; it suffices to note that records made from the heart of this form by arranging in various ways, so that a thread hooked into one of the lateral arteries may be attached to a cumbersome recording lever, gives a very inadequate representation of the contraction. Small myocardiographs recording by means of Frank capsules were used in the experiments here described, and the arrangement of the apparatus was essentially the same as described by Wiggers (2) and used for analyzing the contraction process in mammalian auricle. The method of adapting it to the *Limulus* heart was as follows: The myocardiograph arms were adjusted to a given segment so as to exactly span the width of the heart at the end of diastole. A fine silk thread was then passed through the superficial layer of the heart at the lateral borders and the arms of the myocardiograph tied thereto. In this manner there was slight traction on the heart until it began to contract.

Moreover, there was very little resistance offered to the shortening as the myocardiograph and also the Frank capsule were covered with very thin rubber membrane.

The record obtained is that of the mid-segmental shortening, the part of the heart that normally exhibits greater contractility than the inter-segmental portions where the ostea are located and in the anterior part the lateral arteries are attached.

The myogram of different segments. In considering the relation of the heart of the Limulus to its circulatory system it will be noted that the five anterior segments are each connected with outgoing pathways for the blood. If one reasons from analogy to the mammalian heart, a greater contractility should mark the myogram of these parts as compared with that of the posterior segments.

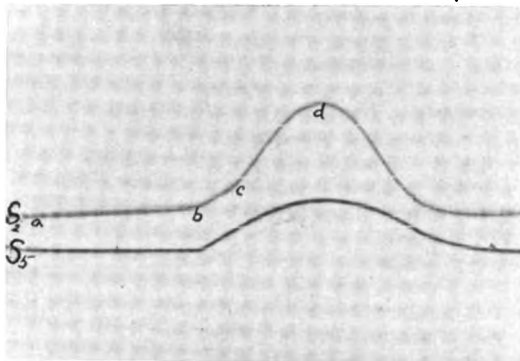


Fig. 1. Simultaneous myograms from heart segments 2, S_2 , and 5, S_5 , showing differences in the contour of the curve from these parts.

A comparison of the myogram from the two ends of the heart, for example, segments 2 and 8, shows differences in the contour, but the curve from segment 5, which has lateral openings, does not exhibit significant difference from that of segment 6, which has no such openings. It appears, therefore, that specialization in contractility, such as is shown in the ventricle of the mammalian heart, is not sharply delimited in the heart of the Limulus to that part from which the circulating fluid is outgoing.

The contraction amplitude is nearly always greatest in segment 2. The myogram of this segment, in figure 1, shows a small primary rise, b to c , upon which is superposed the main contraction, c to d . The upstroke of the principal rise is rapid and the summit is relatively

pointed, indicating that the state of maximal contraction occurs in all of the elements of this segment at practically the same instant. All of these features are exhibited in the myogram of segment 3, excepting that the degree of contraction is usually a little less. The myograms of 4 to 8 all show a smooth rounded contour and, barring differences in the amplitude, the curves from these different segments are practically superimposable. The shortening process in these segments develops slowly, as is shown fairly typically in the myogram of segment 5, figure 1, and moreover the maximal shortening is reached gradually, giving the curve a flattened summit. These features indicate that the contraction takes place in a wave-like manner; some of the elements at the beginning of systole are contracting while others are quiescent, while at the end of systole some are undergoing relaxation while others are still contracting. This form of contraction is suggestive of the type found in the mammalian auricle (2).

In the vigorously acting heart the myograms of segments 2 and 3 are characterized by a slowly developing state of tension preceding the beginning of contraction. This is shown in the myogram of segment 2, figure 1, in the part of the curve from *a* to *b*. The diastolic phase continues so that the curve passes somewhat below the level at the beginning of systole. Then follows the state of developing tonus during which the curve gradually swings back. In a slowly beating heart the curve reaches the level before the next systole begins, but with a more rapid rhythm the tonus increase extends right into the next systole. These presystolic tonus changes have not been found in hearts exposed for an hour or more to experimental procedures; they have also not been exhibited in the records from the posterior segments.

The sequence of segmental activity. Inasmuch as the experimental evidence for the *Limulus* heart favors the view that the impulse is initiated in the median ganglion, the precise time of activity in different segments is a matter of some interest. A casual inspection of a pulsating heart gives the impression of a simultaneous event throughout the nine segments. Carlson (3) states that "when an empty heart has been beating for several hours, or till nearly exhausted and the rate of the pulsations is in consequence much reduced, it can be made out . . . that the contractions start in the posterior third of the heart and travel anteriorly. . . . This is evidently the case in the fresh and vigorous heart." In a later communication the same writer (4), discussing the degree of automatism of different parts of this heart, attributes this function primarily to the middle third, in a less degree to the posterior third, and least in the segments of the anterior third.

From the foregoing statements it is evident that the question of segmental sequence can be answered only by exact measurements of initial activity in different segments. This has been done by simultaneous myograms of selected parts of segments, and by myograms related to the wave of excitation as detected by a string galvanometer. The usual procedure of taking simultaneous myograms was to attach one myocardiograph to segment 2 and a second to segment 3, then after a short interval records were taken. One myocardiograph was then changed to the next segment and the process repeated, and in a similar manner records were taken from all segments. Usually only one series was taken from a heart and sometimes only a few segments were compared, but each record was taken in duplicate and the mean of these was used in making up the data for that experiment.

In general the results show that the middle segments, that is, segments 4 and 5, exhibit activity in a given cycle earlier than the posterior or anterior segments. A comparison of the beginning of contraction of segment 5 and of segment 2 in sixteen experiments shows that segment 5 preceded by an average interval of 0.046 second. In nine experiments comparing segment 2 with segment 4 there is shown an average time interval of 0.047 second, with segment 4 preceding. This indicates that the beginning of contraction in segments 4 and 5 is practically simultaneous and that it normally precedes the contraction of segment 2. On the other hand, a comparison of segment 2 with segment 6, for example, shows in eight experiments an average difference of 0.023 second, indicating that while segment 6 slightly precedes the beginning of contraction of segment 2, it follows by an average interval of 0.024 second the contraction of segment 4.

A comparison of the initial activity in segments 7 and 8 by this method has given less satisfactory results because of the usually low degree of contractility which makes it difficult to determine precisely the beginning of shortening. It is possible, therefore, to make only a general statement concerning them. In six experiments comparing the beginning contraction of segments 2 and 7, it is shown that segment 7 precedes that of segment 2 in four instances and follows it in the remaining two. In a similar way, the data for seven experiments comparing segments 2 and 8 show that the contraction of segment 8 preceded the contraction of segment 2 in three instances and followed it in the remaining four. This indicates that the contraction of the posterior segments normally takes place at practically the same time as the anterior ones.

The records, when viewed as a whole for the seven experiments of the series and the successive stages in each compared, show moderate changes after about 3 hours of the alternate occlusion and deocclusion. All of the experiments were continued for approximately 4 hours. The final contour of the pressure curve usually takes the form of a marked primary oscillation followed immediately by a sharp decline of the curve replacing the systolic plateau of the normal curve. These features are quite characteristically shown in the three segments reproduced in figure 1, in which corresponding points in the curves are indicated by similar letters. These curves were taken as follows: *I* at the outset of the experiment; *II* at the end of 2 hours and 20 minutes during which the alternate 20-minute occlusion and 5-minute release of two femorals

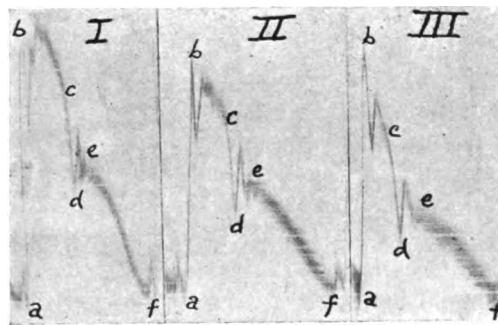


Fig. 1. Segments of the optical arterial curves during the progress of successive occlusion and deocclusion of the veins of three extremities.

and one brachial veins were carried out; *III* at the end of 3 hours and 40 minutes of alternate occlusion and release.

The change in mean blood pressure taking place in this period is slight, but significant in view of the fact that the directional change is downwards and that the optical curve is indicative of lowered peripheral resistance. The following table will assist in bringing out this feature of the blood pressure change and also the time of appearance of a marked change in the form of the pressure curve. This table shows that averaging the interval before a marked change was apparent in the contour of the pressure curve there was required about $3\frac{1}{2}$ hours of alternate clamping of the veins or ligating of the extremities and that much longer time was necessary to give unmistakable signs of decreased peripheral resistance. Definite indications of circulatory failure and

a shock-like condition were shown, however, in only one instance, that of experiment 8, but the data for this experiment give ground for the view that the occlusion effects per se played a relatively less part than trauma of the sensory nerves from application of the ligatures. There were marked sensory signs with each application of the ligatures and mean blood pressure in the early part of the experiment rose from 172 to 206 mm. Hg.; then occurred a fairly sudden break and a fall in pressure. The optical curve does not give indication of increased resistance as the main cause of this rise; it is probably due, therefore, to an increased cardiac output.

Thus, however viewed, the alternate occlusion and deocclusion of the circulation of three extremities fails to effect changes in the dynamics of a more pronounced character than have been shown to occur in the

TABLE 1

EXPERIMENT	BLOOD PRESSURE		LENGTH OF EXPERIMENTAL PERIOD		ONSET OF CHANGE IN PRESSURE CURVE		STATE OF ARTERIAL RESISTANCE AT FINISH
	At the start	At the finish	hours	minutes	hours	minutes	
1	106	110	5	50	3	45	Decreased
2	74*	118	3	45	3	15	Decreased
8	172	88	4	30	3	25	Very low
10	132	114	3		2	10	Decreased
11	152	132	3	50	3	20	Decreased
14	166	112	5		3	45	Decreased
15	126	112	4				No change

initial stages of circulatory failure of shock (2) and a period well over 3 hours is required for this change to appear.

Clamping of the inferior cava: The moderate degree of change in the pressure curve resulting from occlusion of the circulation of the extremities suggested extending the procedure to include larger vascular areas. It is interesting to notice in this connection that the minute volume flow to the posterior extremities, as calculated from the flow in the femoral vein (7), is 45 cc. There are no data available concerning the supply to the anterior extremity but it is usually assumed to be approximately equal to that of the posterior extremity. The three extremities, therefore, would represent a volume flow of 135 cc. per minute. On the other hand, it has been shown that the kidneys have a minute volume flow of 195 cc. for the two organs (8). These data represent average normal values and at best are only approximate,

but they serve to indicate that the clamping of the cava affects a many times greater vascular field than was included under the experiments on three extremities.

The pressure changes following cava obstruction indicate in a striking way that there is a greatly diminished venous return which causes some cardiac embarrassment. There is a reduction in the amplitude of the curves with a retardation in the gradient of the upstroke and the end of systole is not sharply marked by a distinct incisura. With the first deocclusion of the cava there is evident in the pressure curve a resumption of the main characteristics of the original, but after the second period of clamping little tendency to recovery is shown; furthermore, there is indicated a marked relaxation in peripheral tone. The total time of occlusion of the inferior cava necessary to give these indications of a break in the dynamics was never more than 1 hour. It may have been somewhat less since the periods of occlusion were from 25 to 30 minutes.

The results of one experiment in which the clamp was applied just posterior to the inlet of the renal veins is of interest, since in this manner the kidney circuit is left intact. The blood pressure fell about 30 mm. Hg. when the clamp was on but showed practically complete recovery each time it was removed. This was repeated four times, covering a period of 2 hours and 10 minutes, and at the end of this time the optical curve showed the characteristics of initial failure. There is suggested, therefore, a degree of proportionality between the time of appearance of these circulatory changes which influence the form of the pressure curve and the extent of the vascular field occluded.

Occlusion of the inferior mesenteric vein: The inferior mesenteric vein drains an entirely visceral area in contrast to the conditions considered above. Moreover, it represents a vascular field as indicated by the figure for blood flow of 164 cc. per minute (9) quite comparable to that studied under occlusion of the extremities.

The outstanding features in the pressure curve during the progress of this type of occlusion are the relatively sudden appearance of the change in the contour of the curve and the slight indication of progressive development after this initial change. The first period of clamping was about 40 minutes and the pressure curve shows (fig. 2, *II*) at the end of this time a sharp primary oscillation (*a-b*) without plateau (*b-c*) and with low diastolic limb (*e-f*). Each record was taken at the end of the 5-minute period of deocclusion. Segments *III* to *VI*, while differing somewhat in amplitude, show slight changes in their essential

characteristics and give evidence of a comparatively fixed state of dilatation after the first period of stasis. Furthermore, these succeeding periods of occlusion show only moderate depression in blood pressure and nearly identical recoveries during the periods of deocclusion. These changes lend support to the view that the cardiac mechanism is not markedly affected by the degree of reduction in the venous return.

The significant features in these results appear, therefore, as the rapid initial decrease in blood pressure with comparatively small changes from the alternate periods of occlusion and deocclusion, and the slight tendency to a progressive type of change in the pressure curve. Many factors are concerned probably in the production of the effects following occlusion of the venous return from such vascular areas, but the

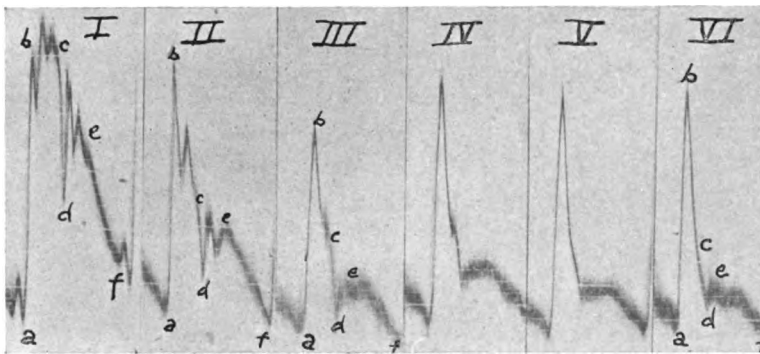


Fig. 2. Segments of optical arterial curves during the progress of successive occlusion and deocclusion of the inferior mesenteric vein.

following warrant special consideration: (a) Mechanical distention of the blocked venous system; (b) a toxic action of products formed in the stagnant areas which exert further injurious effects when periodically flushed into the circulation; and (c) the damaging of the vascular walls with accompanying alterations in permeability. The present experiments do not permit of direct conclusions concerning which of these factors plays the essential rôle in the production of the effects studied. Indirectly they give evidence, however, in favor of the view of mechanical dilatation as the main cause of these primary changes, since it has been shown that occlusion of an intestinal area which affords by virtue of its plastic character a favorable site for mechanical stretching of its vascular walls, is immediately affected and the change appears almost in full magnitude at the outset. The occlusion of a peripheral

field of comparable vascular magnitude, which presents a comparatively rigid vascular area, gives results essentially different in that corresponding changes in the pressure curve appear much later in the course of events.

Thus far, no account has been taken of the possible toxic effects of substances formed during the periods of stagnation. In order to throw light directly upon the probable degree of influence which substances of this character exert the experiments below with histamine were performed.

Successive injections of histamine: The results of Dale and Laidlaw (10) show quite conclusively that the administration of histamine may produce a condition simulating traumatic shock. This phenomenon

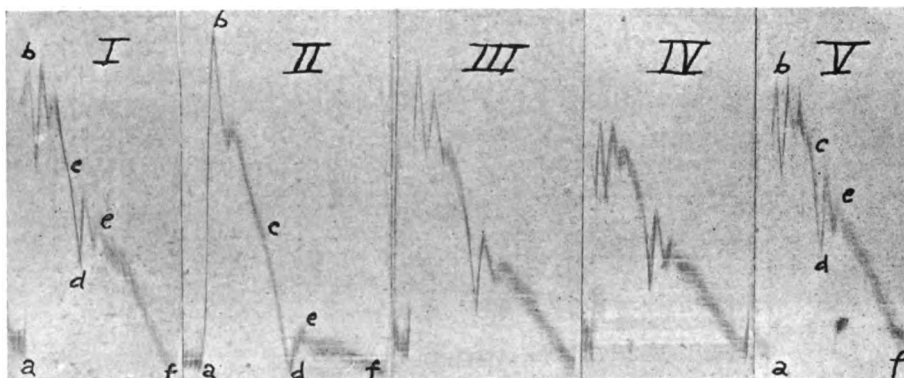


Fig. 3. Segments of optical arterial curves at certain stages during the blood pressure change from injection of 0.15 mgm. histamine. The numbering of segments corresponds to positions indicated on figure 4.

they assign to increased capaciousness through the relaxation of capillary tone from the toxic action of this substance. In their experiments cats were used for the most part and a dosage of a milligram per kilo body weight was found necessary to produce circulatory collapse.

In the present experiments on dogs it was sought to test not only the immediate effects but also the accumulative action of histamine on the dynamics of the circulation; accordingly, the injections were usually 0.04 or 0.05 mgm. (the ergamine of Burroughs, Wellcome & Co.) repeated at 10-minute intervals over a period of 3 to 4 hours. Such a dosage never fails to give at each injection a fall of over 50 per cent in blood pressure at the start. The recovery is rapid at first and usually complete in less than 3 minutes but as the experiment progresses and

also following larger injections a somewhat longer time is required before the pressure returns.

In figure 3 are shown portions of the optical records taken during the changes produced by the injection of 0.15 mgm. histamine. These curves, taken in connection with the tracing of the blood pressure change shown in figure 4, portray the immediate effects of this substance upon the pressure relations. Coincident with the fall in mean blood pressure the optical curve shows (fig. 3, segment *II*) a large primary oscillation

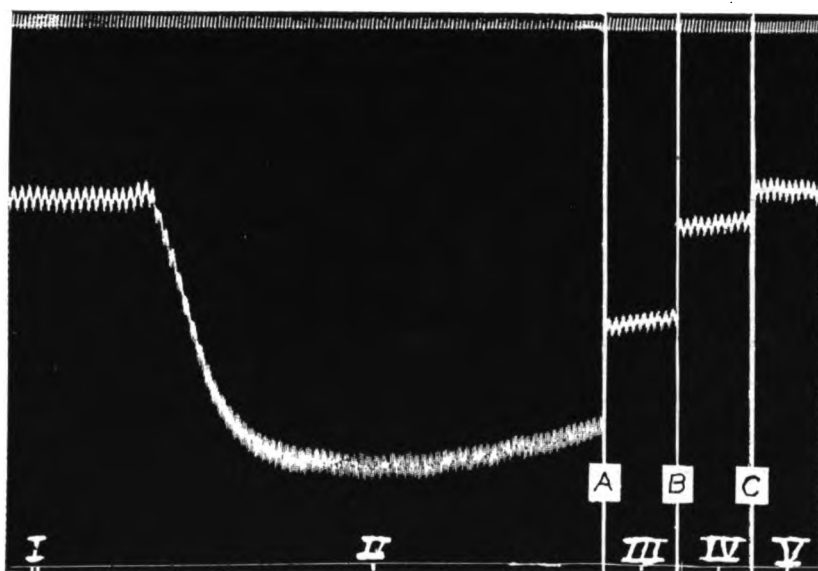


Fig. 4. Tracing showing blood pressure change as related to optical curves in figure 3. Numerals correspond to segments in that figure. The intervals A, B and C correspond to 2 minutes, 5 minutes and 5 minutes, respectively. Time curve indicates seconds.

(*a-b*), indicative of a collapsed state of the arterial system (*c-d*), and a flattened diastolic limb (*e-f*), signifying a low state of peripheral resistance. There is a rapid restoration of peripheral tone indicated in segment *III*, *e-f*, by the immediate rise in this portion of the curve. This change in resistance suffices to restore mean blood pressure in a short time but it will be seen from segment *IV* that the recovery of the dynamic relations is complete before mean blood pressure has reached its original level. The extent to which cardiac output is influenced by

these changes does not appear from the present data. Further experiments dealing with this feature are in progress.

Turning now to the influence of the successive injections, it was demonstrated at the outset that small doses, e.g., 0.01 mgm. per injection, have little accumulative effect. With individual injections in amounts of 0.05 mgm. it has been possible generally to produce in dogs of about 8 kilos signs of initial circulatory failure after a total of 0.5 to 0.7 mgm. had been injected in the manner indicated. The stages in the failing dynamics are very well brought out in figure 5. Segment *I* was taken at the outset of the experiment and serves as a basis for comparison; segment *II* was taken after seven 0.04 mgm. injections had been given; and segment *III*, after thirteen such injections. Close

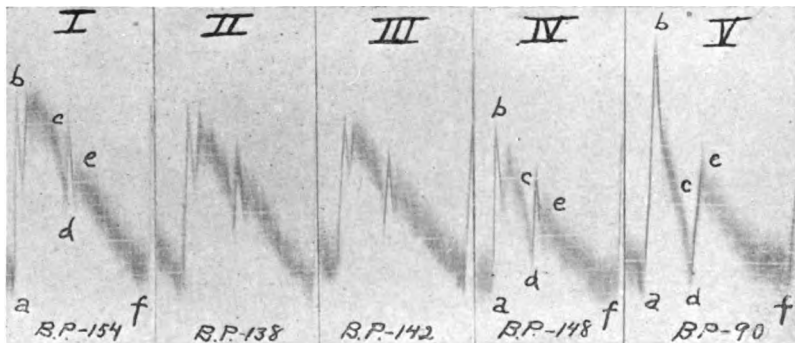


Fig. 5. Segments *I*, *II*, *III* and *IV*, optical arterial curve during progress of successive injections of histamine. Segment *V*, taken 25 minutes following injection of 5 cc. adrenalin (1:5000). Description in text.

inspection of these curves shows a sharper contour in *II* and *III* and a slight diminution in the height of the primary oscillation. These features are significant in that they anticipate the more marked changes characteristic of failing peripheral resistance and that they take place without significant changes in mean blood pressure. At this stage of the experiment the dosage was increased. There followed two 0.2 mgm. injections at the usual 10-minute intervals and one injection of 0.5 mgm. Whereas the smaller amounts had usually caused a fall in blood pressure to 50 to 60 mm. Hg., the latter dose depressed the pressure to 36 mm. Hg. Segment *IV* was taken 20 minutes following the 0.5 mgm. injection and at a time when blood pressure had practically recovered. It will be seen that the introduction of the larger amounts augmented the features already noted and that the curve now exhibits

a certain likeness to that shown under the occlusion of the veins to the extremities and characteristic of initial failure.

These results present quite typically the effects on the optical curve of repeated injections of histamine. It is significant to note, also, that all of the experiments were continued for a period of about 4 hours without a single instance of circulatory collapse appearing, notwithstanding injections at the conclusion of some of the experiments of a milligram of histamine following closely upon successive doses only slightly less, with a total given during the experiment amounting to 3 mgm. or more. These observations lend support to the view that the dilatation resulting from the amounts of histamine used, and administered in the manner indicated, causes only moderate dynamic changes. Furthermore, it appears that the change is one that may be due to the reduced resistance from simple capillary dilatation. With the possibility in mind that a moderate vasoconstriction might counteract the effects of the periodic histamine dilatations and thereby restore the failing dynamics, injections of 5 cc. of adrenalin (1:5000) were given at the rate of about 1 cc. per minute. The usual constrictor response followed but passed off in ten to fifteen minutes and a vascular equilibrium was again established. The pressure relations at this stage are very well shown in segment V of figure 5, taken 25 minutes following the administration of the adrenalin. It shows that, notwithstanding a good state of peripheral resistance signified by the height and slope of the diastolic limb, *e-f* of the curve, there is a diminished distention of the arterial system evidenced by the increased amplitude and sharp contour of the primary oscillation, *a-b*.

The marked vasoconstriction of the adrenalin appears to have the effect, therefore, of augmenting the condition started by the histamine. In this connection it is interesting to consider briefly the possible mechanism of action of adrenalin whereby it accentuates the dilatation initiated by histamine. Hartman and McPhedran (11) state that large doses of adrenalin dilate the intestinal vessels. On the other hand Erlanger and Gasser (12), while not able to agree with this conclusion, point out that portal pressure is greatly increased by giving large amounts.

The results presented above give unmistakable evidence of a decrease in peripheral resistance after repeated small doses of histamine. It is well to bear in mind that several factors may contribute to this end, important of which are decreased arterial tone, dilatation of the capillary areas and decreased viscosity of the blood. While it is not possible

to state with certainty regarding which of these factors plays the greater rôle in the reduction of peripheral resistance with histamine, it is reasonable to assume that the action of adrenalin described above is due to a further dilatation of the weakest link in the vascular circuit. The usual absence of reduction in arterial tone from adrenalin, and also the excellent results of Dale and Richards (13), indicating that histamine is a capillary dilatant; support the conclusion that the capillary system is the part less resistant and is the area which compensates for the intense constriction of the adrenalin. The data at hand do not indicate whether this effect is mainly on the intestinal area or is generally present in the capillary blood-bed of all organs. The observation of a great increase in portal pressure lends support to the view that the area supplied by this vessel may play the larger part in these results.

One point still remains to be discussed; that is, the bearing of the results with histamine upon the effects following occlusion of different vascular areas. The optical curves show features in common, each presenting changes indicative of initial failure of normal dynamic relations. It might appear, therefore, that the occlusion effects were caused by metabolic products with histamine—like action formed during the periods of stasis. There seems little doubt that such products may contribute to the effects of occlusion, but that they are not the main cause is evidenced, I believe, by the relatively large amounts of histamine necessary to initiate failure changes and by the observation recorded above that during the periods of reëstablished circulation through the occluded part there are never indications of a dilating substance being carried into the general circulation.

SUMMARY

1. Alternate periods of occlusion and release of the circulation of three extremities, when continued for about 4 hours, produce changes in the optical pressure curve comparable to those shown in initial circulatory failure. There appears to be little difference whether the occlusion is produced by *a*, ligating all of the limb structures except the main arterial supply; or *b*, clamping the principal venous channels from these organs.

2. Clamping the inferior cava anterior to the renal veins shows indications in the pressure curve of cardiac embarrassment from diminished venous return. Two 30-minute periods of occlusion of this vein interrupted by 5-minute intervals of reëstablished flow produce

marked changes in the dynamic relations. By lessening the vascular area blocked, the time of appearance of these changes is somewhat delayed.

3. Blocking the venous return from a visceral area brings on a failure type of pressure curve much sooner than occlusion of a peripheral area of comparable vascularity.

4. The observations of a slow, progressive development of the occlusion effects of peripheral structures, the rapid onset with little evidence of progressive development for visceral areas, and the character of the changes portrayed in the pressure records, support the interpretation that the cause is essentially one of mechanical distention of the blood-bed in the occluded parts.

5. The optical pressure curves during the blood pressure change from a small dose of histamine show a sudden decrease in the peripheral resistance with a greatly diminished arterial distention, and an immediate recovery of peripheral tone. Injections of 0.04 to 0.05 mgm. repeated at 10-minute intervals produce after many such doses a small degree of decrease in peripheral resistance. Larger doses serve to accentuate these initial effects of the periodic dilatations.

6. Adrenalin augments the failure changes initiated by the repeated histamine injections.

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- (4) ROY AND BROWN: Journ. Physiol., 1879, ii, 323.
- (5) MANN: This Journal, 1918, xlvii, 248.
- (6) ERLANGER AND GASSER: This Journal, 1919, xlix, 151.
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Fundamental Ideas Regarding Basal Metabolism

GRAHAM LUSK, PH.D.
NEW YORK

FUNDAMENTAL IDEAS REGARDING BASAL METABOLISM *

GRAHAM LUSK, PH.D.
NEW YORK

As early as 1839, Sarrus and Rameaux¹ stated that, since the loss of heat in animals must be proportional to their surface area, therefore the heat production must be proportional to the same unit.

Regnault and Reiset,² ten years later, wrote:

The consumption of oxygen absorbed varies greatly in different animals per unit of body weight. It is ten times greater in sparrows than in chickens. Since the different species have the same body temperature, and the smaller animals present a relatively larger area to the environmental air, they experience a substantial cooling effect, and it becomes necessary that the sources of heat production operate more energetically and that respiration increase.

Only three years after this, Bidder and Schmidt³ made the following thoroughly modern statement:

The extent of the respiration, like every other component of the metabolism process, is to be regarded as a function of one variable, the food taken, and one constant, a distinctly typical metabolism (*Respirationsgrösse*) which varies with the age and sex of the individual. This factor characterizes every animal of a given race, size, age and sex. It is just as constant and characteristic as the anatomic structure and the corresponding mechanical arrangements of the body. It is in the main determined by the heat consumption in the organism; that is to say, the replacement quota for heat lost to the body through radiation and conduction to the environment in a given unit of time. It may therefore be used to determine this, or in case the factor of heat loss is known, one can deduce the extent of the metabolism.

* Read before the joint meeting of the Section on Practice of Medicine, the Section on Pharmacology and Therapeutics, and the Section on Pathology and Physiology at the Seventy-Second Annual Session of the American Medical Association, Boston, June, 1921.

1. Sarrus and Rameaux: *Bull. Acad. roy. de méd., Paris* 3: 1094, 1839.

2. Regnault and Reiset: *Annales de chimie et de physique, Series 3* 26: 299, 1849.

3. Bidder and Schmidt: *Die Verdauungssäfte und der Stoffwechsel*, Mitau and Leipzig, 1852, p. 348.

This typical metabolism . . . is that of the fasting animal. It must be nearly the same in animals having the same body volume, surface and temperature; the larger the body surface, the body volume and temperature remaining constant, or the higher the body temperature with surface and volume constant, the higher will be the metabolism as determined by the laws of static heat.

Of course a sharp mathematical treatment of this phenomenon can be thought of only after very numerous and exact experimental determinations on animals of most varied form, size and temperature.

Rubner⁴ first applied exact calculations to this problem, and he announced that dogs varying from 3 to 30 kg. in weight produced the same number of calories per square meter of body surface, though per kilogram of body substance the heat production was 88 calories per kilogram in the smallest dog and only 36 calories per kilogram in the largest one. He remarks:

Large and small dogs do not metabolize different quantities of food because their cells are differently organized, but because cooling influences on the skin excite the cells to activity.

Shortly after Rubner's publication, Richet, in 1885, showed that a cat, a rabbit and a goose, all of similar weights, produced approximately the same amounts of heat. He stated that in future one should express all calorimetric observations in terms of surface area and not in weight, a principle now very largely followed in the United States.

Rubner later came to a better understanding regarding the cause of the Law of Surface Area. He found that two guinea-pigs of different sizes had the same heat production per square meter of surface, even though they lived surrounded by air at a temperature of 30, thus excluding all thermal influences. He realized from this that the level of the basal metabolism could not be caused by the influence of cooling on the body, and no one has since thought so. Rubner,⁵ however, stated that he believed that the phenomenon observed was the result of accommodation to the action of cold to which animals in former ages had been exposed.

4. Rubner, M.: *Ztschr. f. Biol.* 19: 549, 1883.

5. Rubner: *Die Gesetze des Energieverbrauchs bei der Ernährung*, Leipzig and Vienna, 1902, p. 174.

My own work has shown that a cold sugar solution, introduced into the stomach of a dog, can induce an extra production of heat extending over several hours. The body can therefore still respond to a withdrawal of heat by a compensatory production of it.

Rubner calculated the surface area of animals by the formula of Meeh,⁶ published in 1879. This formula assumed that the surface was a function of the $\frac{2}{3}$ power of the volume. Since animals contain the same materials, weight may be substituted for volume. The result thus obtained was multiplied by a constant k which expressed the relationship of weight in kilograms to surface in square meters for a given species. For man, the formula of Meeh was $12.3\sqrt[3]{\text{(body weight)}}$.² It may be noted here that Dreyer, Ray and Walker⁷ found that the surface area, blood volume and cross sections of the aorta and of the trachea are all proportional to the $\frac{2}{3}$ power of the weight. Dreyer later concluded that the vital capacity was a simple function of the body surface. Moulton⁸ found that the surface area was a two third power function of the total body nitrogen of beef cattle and, therefore, of the protoplasmic mass. This confirms the conclusion of Carl Voit that the mass of the cells and their power to oxidize materials determines the height of the metabolism. One should remember, however, in this relation the fact that in very corpulent people the heat production appears proportional to the surface area and not to the mass of protoplasm.

Using Meeh's formula, McCrudden and I,⁹ in 1912, found that the basal metabolism of a dwarf was 775 calories per square meter of surface, and of two dogs 759 and 784 calories, respectively, results which agree within 3 per cent. Comparing these with results obtained by Benedict on four men, it was found that they produced an average of 789 calories per square meter of surface. It was also pointed out that an infant 5 months o'd, investigated by Howland, produced 1,100 calories per square meter of surface in twenty-four hours. This accords with former observations made in 1899 by Magnus-Levy and Falk.¹⁰

6. Meeh: *Ztschr. f. Biol.* **15**: 425, 1879.

7. Dreyer, Ray and Walker: *Poc. Roy. Soc. Series B* **86**: 39, 56, 1912-1913.

8. Moulton, C. R.: *J. Biol. Chem.* **24**: 299 (March) 1916.

9. McCrudden and Lusk: *J. Biol. Chem.* **13**: 450, 1913.

10. Magnus-Levy: *Arch. f. Physiol.*, Supplement, 1899, p. 388.

As early as 1895, Söndén and Tigerstedt¹¹ pointed out that the heat production of children during the period of adolescence was relatively higher per square meter of surface than in the adult. This long-neglected scientific information was confirmed by the contributions of Murlin and of Du Bois, as well as by the extensive and valuable studies of Benedict and Talbot. About this time it was found that the food prescribed by the commonly accepted dietary standards was insufficient for the nourishment of children in the regions of occupied Belgium and blockaded Germany.

With the establishment of the calorimeter of the Russell Sage Institute of Pathology in Bellevue Hospital during the winter of 1912-1913, under the active control of Du Bois, it became absolutely necessary to seek for accurate standards with which to compare the heat production in hyperthyroidism, for example, with the heat which the patient would presumably have produced had he been perfectly well. As there was a lack of accurate data, Gephart and Du Bois¹² investigated the heat production of several normal controls, and in their preliminary work established the value of 34.7 calories per square meter of body surface per hour as representing the basal metabolism of individuals of usual shape when the surface area was calculated by the Meeh formula. Although criticism has been made that protoplasmic mass is the sole criterion of the intensity of metabolism, it appeared beyond the bounds of possibility to determine the protoplasmic mass in hyperthyroidism, whereas the Meeh formula furnished the most ready means then at hand of estimating the surface area. Du Bois at that time came to the conclusion that, although Meeh's formula might not accurately measure the surface area, at least the heat production was proportional to Meeh's formula.

Finally, E. F. Du Bois actually measured the surface area of several individuals, and with his cousin, Delafield Du Bois,¹³ worked out a formula from the measurements obtained. He was thus able to calculate the true surface area within an average error of ± 1.5 per

11. Söndén, K., and Tigerstedt, R.: *Skand. Arch. f. Physiol.* 6: 1, 1895.

12. Gephart, F. C., and Du Bois, E. F.: *The Determination of the Basal Metabolism of Normal Men and the Effect of Food*, *Arch. Int. Med.* 15: 835 (May) 1915.

13. Du Bois, Delafield, and Du Bois, E. F.: *The Measurement of the Surface Area of Man*, *Arch. Int. Med.* 15: 868 (May) 1915.

cent. and a maximal variation of ± 5 per cent. Meeh's formula proved to have an average inaccuracy of 16 per cent. and a maximal variation of 36 per cent., the latter being found in the obese.

The now generally used Du Bois height-weight formula for determining the surface area indicated that the measure of the basal metabolism was 40 calories per square meter per hour in men, and 7 per cent. less than this in women. Du Bois claimed an accuracy of within ± 10 per cent., but of late others have ascribed even a greater degree of accuracy to his method. His body surface formula shows that very obese women, like the one described by Means as being a "veritable pork barrel," conform to Rubner's law that the heat production of the basal metabolism is proportional to the surface area.

Following Du Bois, Benedict and Harris published a book entitled "Biometric Study of the Basal Metabolism in Man," and gave various tables for the computation of the basal metabolism. Using these tables for people of early adult life, the calculations by both methods yield essentially the same results. The average basal metabolism of three old men, as determined by Benedict, was much lower than that found in six old men by Aub and Du Bois,¹⁴ and this tends to throw doubt upon the calculations of the true basal metabolism of old men. It may, however, be added that the basal metabolism of Zuntz remained at a constant level from the age of 41 to the age of 63.

Dreyer¹⁵ has objected to the introduction of the standing height as a factor in the calculation of the surface area on the ground that it is not a physiologic measurement, and he regards the sitting height as a more normal expression. He has evolved a formula which is based on age and weight alone. He states that this formula indicates that basal metabolism is not a simple function of body surface.

However, Dreyer calculates that the deviation between observation and calculation for Benedict's own series is, in the case of males, 5.27 per cent. by his own formula, 5.33 per cent. by Benedict's method, and 5.65 per cent. by Du Bois' method of calculation. These differences, which amount to only 0.38 per cent.

14. Aub, J. C., and Du Bois, E. F.: The Basal Metabolism of Old Men, *Arch. Int. Med.* **19**: 8:3 (May) 1917.

15. Dreyer, G.: *Lancet* **2**: 289 (Aug. 7) 1920.

at most, do not appear to be so considerable as to manifest, for one formula over the others, a readily distinguishable refinement of procedure.

Applying Dreyer's formula to the predictable metabolism of the six old men investigated by Du Bois and Aub, the average deviation from the metabolism actually measured amounts to + 2.2 per cent., whereas Benedict's formula shows a discrepancy of + 19.7 per cent. This, however, is a detail. The main facts are established. The controversy is concerning interpretations and theories.

In a recent publication Benedict¹⁶ pens the following statement:

As a result of the critique of the body surface law presented by Harris and Benedict, we believe that the accurate measurements of body surface made possible by Du Bois may legitimately be used in a manner heretofore never practicable in metabolism experiments, provided that they are considered as physical measurements and with no erroneous conceptions as to the existence of a causal relationship between surface area and heat elimination.

I believe this statement to be somewhat exaggerated. I believe that the Du Bois standards for basal metabolism can be relied on, and I also believe that, though one may doubt the causal relationship between surface area and heat elimination, such doubt will not invalidate the arithmetic employed in the calculation. In making this statement I recall the words of Carl Voit, uttered regarding another matter:

I maintain this as an incontestable fact. It is of itself so important that I question whether it is desirable to add a word of explanation. The results of a properly conducted and properly appreciated experiment can never be annulled, whereas a theory can change with the progress of science.

The establishment of a predictable basal metabolism enabled those working with the Russell Sage calorimeter to interpret the variations from the normal in many diseased conditions and has offered a method now widely accepted throughout the world for a closer clinical diagnosis of several pathologic conditions.

16. Benedict and Talbot: *Metabolism and Growth from Birth to Puberty*, Pub. 302, Carnegie Institution of Washington, 1921, p. 159.

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THE PHYSIOLOGICAL EFFECT OF UNDERNUTRITION

GRAHAM LUSK

Department of Physiology, Cornell University Medical College, New York City

Diogenes Laertius states that the philosopher Heraclitus (born about B.C. 435), despairing of mankind, retired to the mountains where he lived entirely upon vegetables and herbs, became dropsical, and died. In the year A.D. 586, when famine desolated France, a similar diet produced edema and death. Gaspard (16), who records the above, also describes famine and death in Guadaloupe among 4000 negroes, who became completely hydropic upon a diet of plants and mallow herbs.

Gaspard also carefully describes the disastrous famine which overwhelmed west central France in 1817, and which he personally witnessed. During the first three months of the year the inhabitants lived on potatoes, oat bread, bran and other poor foods. When these resources were exhausted the unfortunate people were reduced to existing upon the pasture of animals. Materials such as the oyster plant, wild sorrel, nettles, the patience dock, chicory, thistles, the peelings of tender branches, etc., formed their dietary. This herbage was hashed, cooked and thereby reduced to a pulp, as is commonly done with spinach and sorrel. Such a diet, when constantly taken, always resulted in dropsy of the cellular tissues, without ascites, without icterus, without organic lesions of the liver or other abdominal viscera. Many women stated that their menses ceased. It was later found that the number of conceptions during this period was less than half the number which occurred during the corresponding months of the preceding and following years. The dropsical condition continued throughout the entire period of the use of this diet and did not disappear until the harvest season restored normal human food. For months or even years thereafter some of the individuals exhibited swollen abdomens, or edema of the face, of the legs or of the feet.

Those who were the least vigorous or who had subsisted longest on this diet of herbage died on account of it. Sometimes they perished of starvation at the roadside. Others died, not of famine, but from a kind of indigestion caused by a gluttonous indulgence in barley bread when this became available at the time of the new harvest.

The siege of Paris (54) from September 19, 1870, to January 28, 1871, imprisoned for over 4 months two million French people who endured extreme privation. Especially the old people and the children perished from want of suitable food, the lower classes undergoing untold miseries of hunger and cold. Two months before the end of the siege the supplies of milk and meat were practically exhausted. During the last 10 days bread was rationed at the rate of 300 grams per day per person, with half rations to children under five. The bread contained 30 per cent of flour. "The quality is horrible, black, heavy, miserable stuff, made of flour, oatmeal, peas, beans and rice." Cats, dogs and rats were eagerly devoured. The death rate reached 4465 weekly, or at the rate of 116 per 1000 per annum. Scurvy broke out on account of the dominant diet of bread and rice. Delpech (8) states that the presence of scurvy was directly traceable to the absence of fresh vegetables. In one prison, out of 250 prisoners, 65 had scurvy, of whom 11 died. On January 23, the 127th day of the siege, mobs of poor, starving people were in the streets crying "Donnez nous du pain." The capitulation of the city followed 5 days later upon the complete exhaustion of the food supply. During the 2 weeks following the armistice the death rate averaged 4561 per week in contrast with 1122 per week during the corresponding weeks of the year previous (41).

The following picture of the onset of undernutrition in Germany during the war of 1914-1918, is presented by Rubner (49). The blockade was at first inefficient and there was no change from the normal food supply until April, 1916. For the winter of 1916-1917 the department of food supplies planned to provide rationed foods in amounts which may be contrasted with the quantities actually furnished, as follows:

	AS PLANNED			AS ACTUALLY PROVIDED		
	Amount	Protein	Calo- ries	Amount	Protein	Calo- ries
		<i>grams</i>			<i>grams</i>	
Bread.....	271.0 gm.	17.2	688	271.0 gm.	17.2	688
Potatoes.....	710.0 gm.	14.9	710	357.0 gm.	7.5	341
Butter and margarine	18.0 gm.		140	11.4 gm.		89
Milk.....	200.0 cc.	6.8	111			
Meat.....	70.0 gm.	10.7	158	36.0 gm.	4.5	78
Eggs (per piece).....	0.3	4.2	53	0.07	1.0	13
Sugar.....	32.0 gm.		125	26.0 gm.		104
Cereals.....				9.8 gm.	0.9	31
Totals.....		53.8	1985		31.1	1344

The reduced allowance was not everywhere obtainable. In the cities only a third of the quantity of meat allowed was distributed, and in mid-winter 2.5 kgm. of turnips weekly were substituted for a ration of 2 kgm. of potatoes. Additional unrationed foods could be purchased at high prices.

The exclusion of animal foods from the diet made it monotonous, and for the many it was no better than the fare of prisoners sixty or seventy years before. Garnishings, spices, in short all things which might have served to improve the flavor of the food, were lacking. Soups, vegetables, and above all, turnips were the dominant note. The chief characteristic of this diet was its high water content, due to the absence of fat, which was replaced by carbohydrate foods. Such foods, with the exception of bread, are largely diluted with water. Sugar, which usually serves to concentrate the food value of many dishes, was allowed in too small quantities to be of much service.

Rubner remarks that the first result of an insufficient diet is a decrease in the efficiency of laborers. This is evidenced by the fact that fatigue comes on more quickly than usual. Not only is there a decrease in the muscular efficiency of paid laborers, but also in people living sedentary lives; the muscular activities which are concerned with the normal preservation of health become restricted. The love of roaming and of sport is lost, children cease to play, and a person avoids as far as possible all bodily exertion. The mood of the individual affects the result. Thus one may, by special effort, overcome the sensation of fatigue for a certain number of days in order to accomplish a definite result, as does the soldier who advances by magnificent forced marches in anticipation of victory. But this is a very different matter in comparison with the accomplishment of work in the dull, monotonous daily grind of civilian life. During the war certain Italian farm laborers, receiving 450 grams of flour daily, accomplished their work. When this ration was cut to 250 grams they refused to work.

The same apathy is true as regards mental work. The love of accomplishment, the power of performance, the note of personal initiative are absent, which impulses under ordinary conditions increase the assimilation of food and favor muscular energy. As the mind becomes depressed, muscular movements become slow and listless. It is related that a distinguished mathematician of Leipzig, in order to conserve his food requirement, remained in bed most of the day, doing his intellectual work while in bed.

Rubner estimates that the amount of nourishment which should be taken daily by an average adult contains: Calories, 2569; Protein, 91 grams. The official ration offered, in contrast, only one-half the calories and one-third the protein required. Furthermore, bread made from wheat milled at 95 per cent extraction showed a loss of 40 per cent of its nitrogen in the stools, even in strong, healthy men accustomed to rough fare. A bread intended for the use of prisoners and made of rye, maize, and potato-flour showed a loss of 47.3 per cent of its nitrogen in the feces. The mixed diet of peace time showed a loss of 10 per cent of nitrogen, while the coarse, vegetarian war diet showed that 20 or even 50 per cent of the nitrogen of the diet could not be absorbed.

Life under these conditions, Rubner estimated, caused a reduction in body-weight among those of the urban population who were over 25 years of age from an average weight of 60 kgm. to one of 49, or a loss of very nearly 20 per cent.

The Prussian authorities estimated the increase in the civilian death rate as follows:

YEAR	NORMAL = 100	DEATHS ABOVE THE NORMAL RATE
1913	100	
1914	100	
1915	100	
1916	114	
1917	132	280,000
1918	137	294,000

On this basis 800,000 deaths were computed as ascribable to the blockade and its consequences. The validity of the interpretation requires assessment, but it is certain that under-nutrition diminished physical and mental power, reduced resistance to disease, and also that the evils of the time were furthered by lack of warm clothing, lack of coal for heating purposes, and to extreme mental excitement.

It will be recognized from the above general descriptions of partial famine that it is akin to the undernutrition among the poor of large cities prior to the war.

Protein metabolism. The functional activity of living matter is primarily due to the arrangement of protein in protoplasm. A wasted organism, with diminished muscle tissue, is a characteristic result of protein undernutrition. The minimum quantity of protein destruc-

tion in the human being is to be found after giving, during a long period of time, a diet containing sufficient calories, at least one-third of which must be in carbohydrate, preferably in sugar, but which contains no protein. The urinary nitrogen may thus be reduced to only 2.2 grams daily or even less. This level of protein metabolism has been termed by Rubner the "wear and tear" quota of protein metabolism. More recently he (50) has defined it as being the zero point of protein metabolism.

The "wear and tear" quota includes the protein required for the growth of the hair, nails, epidermis and epithelia; it includes the losses through the digestive juices and through the wear and tear on all the organs of the body, especially the daily destruction of protein involved in the demolition of the cellular elements of the blood. It is increased in menstruation, pregnancy and lactation, but is unchanged in old age.

Muscular work is without influence upon this factor.

Rubner calculates that the "wear and tear" quota of protein metabolism corresponds to 0.044 gram of nitrogen per kilogram of body weight daily, or 0.0303 mgm. per minute, an infinitesimal quantity. Since a well-nourished man of 70 kgm. contains approximately 2100 grams of nitrogen, and the wear and tear quota corresponds to about 3 grams of nitrogen daily, one may estimate an inevitable daily loss of 0.14 per cent of the total body protein, unless food protein is furnished with which to repair the machine, to replace the worn-out parts.

Rubner states that under certain conditions a diet containing only 4 grams of protein nitrogen will protect the body from losing protein nitrogen, consequently 1 gram protein may protect 525 grams of body protein from loss of substance. However, should the protein in the diet contain only 3 grams of nitrogen, then on the first day of the diet 1 gram of body protein N would be lost; thereafter the nitrogen loss would be constantly less until finally equilibrium would be reached with 3 grams. Assuming the mean loss during this period to have been 0.5 gram of nitrogen daily and the total loss 525 grams, it is obvious that it would require 1050 days or nearly 3 years to deplete the body of a quarter of its protein store. Biologically the nitrogen minimum is a protective mechanism of the cells against their destruction. This is an important theoretical conception of Rubner's clear-visioned, scientific mind.

To accomplish nitrogen equilibrium at a low level of nitrogen intake it is necessary to provide protein of a chemical composition similar to that of the protoplasm which is being disintegrated. It is in this

particular that a dietary may lamentably fail. For this reason meat and more especially milk are sought. Rubner, in a personal letter to me, states that the decline in the health of the German people was coincident with the falling off of the milk supply (see p. 547). During (11) has written of the importance of the milk question in Austria. He makes the striking statement that the milk supply of Germany in normal times had nearly twice the monetary value of the output of all the German mines, inclusive of coal.

The loss of body protein. A characteristic of undernutrition is a prolonged loss of body nitrogen when the caloric content of the food is insufficient to cover the needs of the individual. This was first indicated by the work of Landergren (35).

Of striking interest and importance in this connection is the work of Jansen (27) upon normal and healthy medical students occupied in the Munich medical clinic of Friedrich Müller. Fifteen such individuals were given the official food ration containing 1600 calories and 60.6 grams of protein (9.7 grams of N). Nitrogen balance experiments were carried out upon them for between 6 and 31 days during March, 1917. Prior to the experiments the men had been for some time on short rations, especially as regards the protein element. The average loss in weight since the beginning of the war had been about 5 kgm. The average weight of the subjects was 62 kgm. While partaking of the above dietary the men lost weight daily and also about 2 grams of body nitrogen. This loss could be attributed to a deficiency of calories in the diet, for the addition to the diet of 500 calories in the form of milk-sugar resulted in the maintenance of body weight as well as of nitrogen equilibrium. Also, withdrawal of 900 calories in the form of carbohydrate from the official ration produced an even greater loss of body protein than when 1600 calories were given. These relations are shown on the following page.

Benedict (4) and his co-workers independently made the same discovery. Benedict selected a number of healthy young men inclined to athletic prowess, some of them over-weight for their height, and set about to reduce their weights about 10 per cent. The kind of food taken was an average mixed diet but in lesser quantity than was taken by other men not on the "diet squads." A typical diet sufficient for the maintenance of body weight contained 2559 gross calories and 12.85 grams of nitrogen. A typical day's ration on the reduced diet contained 1555 gross calories and 8.78 grams of nitrogen, of which 3.27 grams were of animal origin.

Influence of the official ration of Munich, March, 1917, upon the protein metabolism of medical students

	AGE	SEX	WEIGHT	DAILY CHANGE IN WEIGHT	FOOD		N IN URINE AND FECES	N BALANCE
					Calories	N		
			kgm.	grams		grams	grams	
1	32	M	57.6	-250	1632	9.72	11.97	-2.25
				+ 0	2105*	9.74	10.29	-0.56
4	23	M	67.0	-250	1630	9.61	11.74	-2.13
				+200	2027*	9.54	9.75	-0.21
12	21	M	63.5	-350	1616	9.89	12.63	-2.74
				+280	2107*	9.65	9.79	-0.14
5	22	M	64.6	-400	1624	9.72	11.29	-1.58
				-200	730†	10.59	14.74	-4.15
9	22	F	61.3	-500	1630	9.61	11.81	-2.20
				-350	736†	10.59	13.77	-3.19
10	25	F	60.4	-380	1630	9.61	9.93	-0.33
				-420	735†	10.59	13.41	-2.81

* Plus 500 calories in milk-sugar.

† Minus 900 carbohydrate calories.

Twelve men (squad B) partook during one week of a diet containing 1534 gross calories, daily eliminated 115 in the feces, 84 in the urine, and therefore utilized 1336 calories, or 87 per cent of the gross energy ingested. They took 8.21 grams of nitrogen, of which 0.89 gram appeared in the feces, leaving 7.32 grams or 89 per cent for other distribution. The protein of the diet was therefore normally digested.

During a period of 3 weeks the twelve men (squad B) partook of food which yielded 1375 utilizable calories and contained 8.19 grams of nitrogen daily. The nitrogen of the urine and feces averaged 11.29 grams per person. Hence, protein containing 3.10 grams of nitrogen, or approximately that present in 100 grams of lean meat, was lost daily from the bodies of these persons during the period of this low caloric intake. This would amount to a loss of about 2.1 kgm. of such protein-containing tissue in 3 weeks. The average loss in weight, however, was 4.4 kgm. or 6.5 per cent of the original body weights. If one calculates that a kilogram of body weight contains 30 grams of nitrogen, then 67.9 kgm., the average original weight, contained 2037

grams. If of this 65 grams were lost from the body, the loss of body nitrogen would have been only 3.2 per cent of the total original quantity present. The body weight had fallen much more rapidly, indicating a removal of fat and water content from these heretofore well-nourished individuals.

Another group of individuals (squad A) underwent a more prolonged and a greater reduction. During 4 months the greatest average loss of body weight in five individuals amounted to 11.2 per cent and, according to the principle enunciated above, it may be calculated that these five individuals, whose loss of body nitrogen was determined during 86 days, averaged 166 grams each or 8.1 per cent of their original nitrogen content. This calculation is imperfect on account of lack of dietary control on Sundays and during the Thanksgiving and Christmas holidays when protein could have been added to the body.

It has long been known that in the last stages of fasting an animal, having exhausted its stores of fat, may subsist upon its previously well-protected protein supply. Conditions analogous to these are reported by Loewy (58) in experiments upon himself. Weighing 64 kgm. in 1914, he lost 12.75 kgm. during 3 years of war or 20 per cent. When taking a diet of 1500 to 1800 calories, containing 7 to 8 grams of absorbable nitrogen, his urine contained on successive days 12.6, 15.6, 12.5, 15.1, 17.0, 16.5 grams. The great waste of body protein of which this was the proof and the physical and mental depression the portent, was entirely stopped by the addition of 200 grams of butter fat to the daily ration. Body protein had been attacked in the absence of any other available source of energy.

Retention of protein. An organism which has been depleted of its protein shows a great avidity for protein deposition when occasion offers. This was long ago shown by Rubner for the dog. Kestner (29) reports results obtained by adding 100 to 120 grams of meat to a hospital diet administered to patients who had suffered from extreme protein hunger. The following example may be cited: Patient J; weight 51 kgm.; slightly nervous female; of ruddy appearance.

	N IN DIET	URINE N	FECES N	± BODY N
Hospital diet (average of 4 days)	8.0	4.5	2.2	+1.3
Hospital diet + 100 to 120 grams meat (average of 3 days)	13.2	4.25	2.2	+5.75

In this case the whole of the protein of the meat was deposited in the depleted cells of the body.

Kohn (32) reports that a woman laboratory helper weighing 47 kgm., who suffered from chronic undernutrition in its most severe form, partook on one day of a diet containing 826 calories and 1.04 grams of nitrogen, and the loss of body nitrogen amounted to 2.57 grams. The addition of a bit of cheese, which raised the nitrogen of the diet to 5.23 grams, caused a *gain* to the body of nitrogen amounting to 1.97 grams on the day following. The animal protein of the cheese not only prevented a loss of 2.57 grams of body nitrogen, but was also sufficient to be seized upon for constructive purposes by the famished cells of the organism.

The urine of the undernourished patient of Kohn showed no abnormalities in the relative distribution of nitrogenous constituents (33).

Fürth (15) finds, however, that the presence of a gram of nitrogen in the urine of people suffering from chronic undernutrition is accompanied by a relatively high caloric value of the dried solids of such

urine. The caloric quotient $\frac{\text{Calories}}{\text{N}}$ was between 9 to 13.3. Since this quotient for urea is 5.42, for uric acid 8.22, for creatinin 11.40, Fürth infers the increased presence in the urine of oxyproteic acids (quotient 38.0) and hippuric acid (quotient 72.4).

Oxyproteic acid is a characteristic urinary constituent when body tissue is being destroyed, and hippuric acid occurs when benzoic acid compounds are present, as in a predominantly vegetarian diet.

Von Hoesslin (22) shows the very great and continued capacity of an extremely undernourished person to appropriate food protein for the development of body tissue. An adequate quantity of food protein is desirable for this purpose, as well as an adequate intake of calories. The following table represents the results obtained upon a person during a period of four weeks. Values are given for 24-hour periods:

	FOOD INTAKE PER DAY			EXCRETA N PER DAY	N TO BODY PER DAY
	Protein	Calories	N		
	grams		grams	grams	grams
First week.....	62	1744	10.1	7.8	+2.3
Second week.....	57	2529	9.1	6.6	+2.5
Third week.....	92	1928	14.8	8.3	+6.5
Fourth week.....	98	2161	15.6	8.9	+6.7

This represents an addition of 124 grams of nitrogen to the body in 4 weeks.

The avidity with which tissues depleted of protein appropriate new protein for constructive purposes has been frequently observed after wasting disease, and a kindred property is also possessed by the tissues of growing infants.

The energy metabolism. The dietary prescribed by Carl Voit for an average laboring man contained about 3000 available calories. During the war the English came to the conclusion that the requirement of the average adult man was 3000 utilizable calories. Allowing for loss through transportation, marketing and spoilage, 3300 calories were estimated as the basis for the calculation of necessary national supplies. These figures were adopted as standard by the Interallied Scientific Food Commission, which also fixed the following relative food values when estimating the needs of a family:

Man.....	1.00	Child 10-13 years.....	0.83
Woman.....	0.83	Child 6-10 years.....	0.60
Boys over 13 years.....	1.00	Child under 6 years.....	0.50
Girls over 13 years.....	0.83		

A recent (1921) study of the diets of the working classes of Vienna by Gibbon and Ferguson (17) shows that the average dietary contains only 2064 calories "per man" per day instead of the necessary 3000.

Forty-nine families were investigated. The lowest energy value was 1269 calories. The fat was taken mostly in the form of margarine. Relief agencies contributed about 500 calories, or about one-fourth of the daily intake. Children between 2 and 3 years of age were 26.5 per cent under normal average weight and 13.6 per cent under the average normal height. Rickets was found in 29 families the caloric intake of which averaged 1885 calories "per man" per day, but was absent in 20 families which partook on the average of 2325 calories "per man." The writers observe, "It is hopeless to expect from a population on such diets the initiative and vigor by which alone the country can be saved from ruin."

Among German farmers O. Blum (7) found no reduction in body weight during the first 3 years of the war, for they received 3200 calories and 101 grams of protein. The men workers in a small town, on the contrary, lost 12 per cent in weight and the women workers 7 per cent, their dietaries having fallen to 2200 calories with a protein content of 54 to 75 grams. This work is confirmed by Loewy and Brahm (36) who showed that at a time when the poor in the cities were receiving 25 to 50 grams of protein and 1400 to 1800 calories and

were losing weight and body protein, country people were doing well upon a diet of bread and potatoes with small amounts of meat, milk and cheese, containing in all 3500 calories and 100 grams of protein. They state that their findings prove that their peace-time conclusions regarding the quantities of food required for human nutrition were correct.

Friedrich Müller, commenting upon this situation writes:

Naïvely thinking man eats food without mental consideration, still less without giving ear to the current nutrition doctrines of Liebig, or Hindhede, or Ragnar Berg, but rather like a wild animal he follows his instinct until he is fully satisfied. He considers himself wrongly dealt with when he is prevented from doing this. It is therefore natural that the self-provider should take care of himself first, of his children, his relatives, his servants, and his cattle, and that he should anxiously hoard for the future. . . . In times of need the struggle for existence takes inconsiderate forms, the interest of individuals clash, and hand in hand with these conditions the moral sense and the sense of right and wrong are lowered.

Most of the food difficulties of Germany occurred in middle-class families, such as teachers, business people and pensioners who could not demand and receive the enormous pay of common laborers.

In German institutions such as prisons, prison camps and insane asylums, the conditions were worse than among those who were free to struggle to obtain foods in excess of the official rations. In such institutions reductions of 20, 30 and even 46 per cent of the original weight were observed as the result of continued restriction to the official ration, which was inadequate for the maintenance of body weight (42). One report ran "The inmates are all dead."

The effect of emaciation upon the energy metabolism. Magnus-Levy (39) first pointed out the great reduction in the heat production which takes place as the accompaniment of emaciation. The results may be briefly recorded in the following table:

	WEIGHT	METABOLISM 24 HOURS	CALORIES PER SQUARE METER PER HOUR (DU BOIS HEIGHT-WEIGHT FORMULA)	REMARKS
	kgm.	calories		
Extreme emaciation	36.2	835	26.6	Low diet
Emaciation	38.0	1077	33.0	Liberal diet
Rehabilitation	52.2	1486	40.5	Liberal diet

It is evident that the reduction of the weight of a man by 30 per cent may lead to a reduction in his requirement of energy by 44 per cent,

a factor of conservation. Allen and Du Bois (1) commented on this fall in metabolism as affecting individuals who are under weight, for they found that twenty "normal controls," selected by Benedict and Joslin (3) for comparison with diabetic patients, proved to have an average metabolism which was 8.6 per cent less per square meter of body surface than the general average among normally nourished individuals. Allen and Du Bois also noted the great reduction of heat production in diabetic patients fasted in accordance with the Allen program of treatment. In Geyelin's diabetic patient, C. K., the original body weight was 74.1 kgm. before the onset of the disease. Calculated on the normal Du Bois standard for human nutrition of 40 calories per square meter of body surface per hour, his basal metabolism would have been 1920 calories daily. After having been the subject of severe diabetes and prolonged undernutrition this individual, when he again oxidized glucose, manifested a basal metabolism of only 1032 calories daily; or 25.4 calories per square meter of body surface per hour. The reduction in body weight had been 43 per cent and in total heat production 46 per cent below the original normal level.

Next in historical sequence come the important experiments of Zuntz and Loewy (57), (58) who for many years had been masters in the craft of metabolism workers. The metabolism records of Zuntz cover a period of 29 years and may be thus epitomized:

Metabolism of Zuntz

YEAR	AGE	WEIGHT	O ₂ CC. PER MINUTE	CALORIES PER SQUARE METER (MEEH) PER DAY
		<i>kgm.</i>		
1888	41	65.2	236	804
1901	54	67.6	231	780
1903	56	67.6	228	773
1910	63	68.5	235	792
1916	69	60.6	198	709
1917	70	59.4	198	723

There was no influence of age upon the heat production up to the sixty-third year of Zuntz's life. Zuntz at the age of 65 was able to sit up all night and personally supervise a metabolism experiment which lasted 24 hours. He was then still physically young. Between 1888 and 1910 the metabolism of Zuntz had varied between 16.4 and 17.3 small calories per minute and kilogram of body weight. The reduction in body weight due to the undernutrition of the war not only

reduced the heat production per square meter of body surface but also the calories produced per kilogram and minute fell to 15.65 in 1916 and 15.9 in 1917.

The experiments upon Loewy tell in part the same story. The necessitous times reduced his body weight from 65 kgm. in 1914 to 57 kgm. in 1916, a loss of 12 per cent. Whereas before the war he produced 726 calories per square meter of body surface and a total of 1429 calories daily, or 22.9 calories per kilogram per day, in 1916 the requirements of his basal metabolism were 631 calories per square meter, a total of 1169 calories or 20.5 calories per kilogram. But in 1917 Loewy's weight had fallen to 51 kgm., a total loss of body weight amounting to 22 per cent since the beginning of the war. In July, 1917, the urinary nitrogen excretion had risen to 17 grams when there were only 7 to 8 grams of protein nitrogen and between 1500 to 1800 calories in the dietary (see p. 530). A higher energy metabolism was the result of the higher protein metabolism, as is always to be anticipated under such conditions. The emaciated body of Loewy under the circumstances produced on July 23, 1917, as its basal metabolism, 758 calories per square meter of surface (Meeh), 25.6 calories per kilogram, and a total of 1307 calories for the day. Zuntz and Loewy compare this result with the finding Zuntz (56) had previously made upon an undernourished dog the energy requirement of which was increased during the later stages of undernutrition, as appears from the following:

	WEIGHT	CALORIES PER SQUARE METER
	<i>kgm.</i>	
Start.....	10.0	931
Eleventh month.....	4.98	631
Twelfth month.....	4.1	921

Presumably, toward the end the body fat failed to supply the requisite energy, and body protein was the sole remaining resource to make up the deficit of energy in the dietary.

It is to be hoped that an experiment like that upon Loewy will not be repeated in the near future, but though it stands by itself, it must be accepted as representing one of the probable contingencies in extreme emaciation.

The work of Benedict (4) and his associates concerned itself with determining the basal metabolism of the healthy young men whose weight was being reduced by administering a diet containing some good animal protein, but decidedly deficient in caloric value (see p. 528).

The results upon the eleven young men composing squad A may be thus summarized:

	DURING NORMAL DIET (3000 CALORIES) SEPTEMBER 29-30	END OF PERIOD WITH RE- DUCED DIET JANUARY 26-27	PER CENT REDUCTION
Basal metabolism in calories (Table 128).....	1686.0	1367.0	19.0
Calories per kilogram (Table 132).....	25.2	22.3	11.5
Calories per square meter body surface.....	940.0	788.0	16.2
Body weight in kilograms*.....	67.0	61.3	8.5

*Calculated from above data.

During the period of reduction the diets usually contained 2000 and later 1500 available calories. The Sunday and holiday periods were uncontrolled.

Of greater import is the result of the sudden reduction in the dietary of squad B. An intake of food stated to have contained 4000 calories daily per man was reduced to one containing 1375 net available calories per man per day, and this lowered dietary was continued for a period of 3 weeks.

While partaking of the normal diet squad B on four different occasions showed measurements of basal metabolism amounting to 40.5, 40.7, 40.3 and 39.6 calories hourly per square meter of body surface (Du Bois formula). The last and most important determination upon this diet showed a value of only 36.8 calories. Benedict writes of this determination, "The possible factors of fatigue and depth of sleep thus entered into this experiment as in no other one in this series."

If one be permitted to assume that the true normal basal values for these men are averages of the two determinations 40.3 and 39.6 calories per square meter, and 1.08 and 1.06 calories per kilogram of body weight, then one may perhaps be allowed the liberty of rearranging Benedict's table 34 and add to it the analysis presented on page 529 of this review. Such a rearrangement gives the following information:

	DURING NORMAL DIET	END OF PERIOD OF 1375 CALORIES	PER CENT REDUCTION
Basal metabolism in calories.....	1745.0	1293.0	32.0
Calories per kilogram.....	25.7	20.4	20.0
Calories per square meter body surface.....	872.0	647.0	27.0
Body weight in kilograms.....	67.9	63.4	6.5
Body nitrogen in grams.....	2037.0	1972.0	3.2

This table shows that the loss of a paltry 65 grams of body nitrogen bears no relationship to the enormous reduction in basal metabolism which follows the ingestion of a diet containing an inadequate content of calories. So not only is there a mechanism of nitrogen minimum, protecting life from destruction (see p. 527), but here also appears a biological adaptation to a lowered energy intake, preventing the exhaustion of the reserve of body fat.

One can compare the results obtained here with the results calculated by Lusk (37) regarding the man who fasted 31 days in Benedict's laboratory:

	BENEDICT'S FASTING MAN	BENEDICT'S SQUAD B
Percentage reduction in basal metabolism.....	29	32
Loss of body nitrogen, grams.....	277	65
Percentage loss of body nitrogen.....	16	3

It is quite extraordinary that the ingestion of a dietary deficient in calories, extending over 3 weeks, should bring down the basal metabolism of well-nourished young men to the same extent as fasting might have been expected to accomplish. A minimal metabolic rate, which is two-thirds that of the normal basal metabolism, seems to be easy to establish and affords another of those striking "factors of safety" of which Meltzer has so cogently written. Whether the reduction be due to a disturbance in the glands of internal secretion, to a diminished secretion of thyroxin in the absence of adequate protein and calories in the diet, for example, is a field for speculation and investigation.

The effects of a normal diet after undernutrition. No satisfactory experiments regarding the effect of a sufficient diet following one which induced undernutrition have ever been recorded in man.

	WEIGHT	CALORIES PER HOUR	R. Q.
	kgm.		
Basal metabolism, normal nutrition.....	9.25	15.5	0.80
Fifteenth fasting day.....	7.45	13.0	0.73
Second day of food containing 14.3 cal. per hour.	7.6	12.6	0.80
Day after food containing 28.6 cal. per hour....	7.9	13.0	0.93
After 8 days of food containing 28.6 calories per hour.....	8.0	13.9	0.88

Anderson and Lusk (2) made the above observations upon the influence of a normal maintenance diet upon the basal metabolism of

a dog before and after fasting. The food was given at one time 18 hours before the metabolism was determined.

Evidently the condition of the body and not a large influx of food on the day previous determines the height of the basal metabolism.

The production of mechanical work during undernutrition. There is no doubt that the well-nourished individual feels a zest for his work, while the under-nourished tries to avoid all work. Walking gives no pleasure to an underfed seamstress nor golf to a half-starved professor.

Important results have been obtained experimentally by Jansen (27) upon men who accomplished heavy work when partaking of an insufficient diet. Three subjects abstained from muscular work for 3 days and then they walked together over level ground distances of 18, 20, and 25 kilometers (11, 12.5, 16 miles) on 3 successive days. This was accomplished in a driving snowstorm, while underfoot there was mud and melting snow, so that tramping was exceptionally difficult and wearisome. The diet remained the same throughout the experiment and contained 60 grams of protein and 1628 calories, the official Munich ration of the time (see p. 528). The labor of making such a walk would not have been great under ordinary circumstances, and yet the subjects returned home each day over-fatigued and exhausted. Each of the subjects on one occasion, was forced to come home by tram-car during the return journey, so great was the fatigue experienced. One of them (Ebert) on his return home fell into a state of prostration through weakness. The skin was pallid, respiration shallow and quickened, pulse small and slow, temperature subnormal, profuse sweating from the whole body surface; there was no acetone in the urine. Another of the subjects gave indications of the same symptoms on the second day. Apathy and psychic depression were present in all three men during the evenings of these days of exertion. The experiments present two different findings as far as protein metabolism is concerned. In one person the protein metabolism was not increased as the result of muscular work. In the other two persons the habitual nitrogen deficit increased about one gram daily above the deficit induced by the low caloric diet. This corresponds to an increase of about 10 per cent in the total protein metabolism. These results may thus be summarized in the accompanying table.

The average weight of the three men at the time was 57 kgm. A complete explanation of the increase in protein metabolism due to work is not possible.

SUBJECT	PERIOD	FOOD		EXCRETA N	BODY N
		Calories	N		
Ebert	Rest.....	1630	9.61	11.83	-2.22
	Work.....	1628	9.54	12.70	-3.16
	Difference.....				-0.94
Legène	Rest.....	1630	9.61	11.55	-1.94
	Work.....	1628	9.54	10.76	-1.22
	Difference.....				+0.72
Beholz	Rest.....	1630	9.61	10.81	-1.19
	Work.....	1628	9.54	11.78	-2.22
	Difference.....				-1.03

Two of the men were subjected to respiration experiments 12 hours after the second and third days of walking. These experiments had to be carried out at so late an interval because the persons concerned were too exhausted immediately after their walks to be satisfactory subjects for experimentation. The experiments yielded surprising results, both as regards the duration of the after-effects of the exercise and the height of the metabolism. For example, the average increase in the basal metabolism of Legène was found to be 50 per cent above the normal, or an increase from 1440 calories to 2160 for 24 hours. High respiratory quotients were noted, the average being about unity. Jansen states that the explanation of this high quotient lay in the irritable condition of the subject. The subjects, who had formerly yielded themselves freely to this form of experimentation, no longer had either the will power or the physical energy requisite for accomplishing an exact experiment and fell into a state of excitement which was manifested by the increased respiratory movements. The ventilation of the lungs was abnormally increased. This would lead to an "Auspumpung" of carbonic acid from the blood which would explain the high respiratory quotient. There must have been stimuli, perhaps organic acids, circulating in the blood, which acted to stimulate the respiratory center.

This clear-cut presentation of disaster following severe labor during undernutrition was presented by Gowland Hopkins to Chittenden and me at a private meeting held in the rooms of the Royal Society in London, March, 1918, as an unanswerable argument against the reduction of the importation of bread for the people of the United Kingdom.

Iltzhöfer (25) explains the great increase in pulmonary ventilation following muscular exertion when taking a low diet containing 1630 calories as being due to an increased susceptibility of the respiratory center to hydrogen ions.

Iltzhöfer (26) has recently published the details of the respiration experiments upon the medical students investigated by Jansen, and shows that another person, when partaking of a normal diet in 1918, gave no indication of increased metabolism following the accomplishment of mechanical work similar in amount to that done by the medical students. An interesting point is brought out by Loewy (58), who found that in his exhausted condition induced by undernutrition (see p. 530), there was an increased production of calories in his body for accomplishing a unit of mechanical work when he walked on a moving platform set at an incline of 22 per cent. For example, in one experiment, after 9 minutes of climbing, 6.5 calories were required to raise 1 kgm. of his body weight 1 meter high, whereas after 35 minutes, 8.6 calories were required to do the same amount of work, an increase of 32 per cent. No similar increase would have been observed in a normally nourished individual. Loewy, who was 57 years old, remarks: "It is not astonishing that an older man, exhausted by undernutrition, should quickly experience an increase in metabolism per unit of muscle work. It is the expression of diminished muscle power or of previous overexertion."

It is evident from these experiments that the human body has no means of economizing energy for the production of work when work is done after emaciation and during undernutrition.

In the case of squad B, investigated by Benedict, the individual men were caused to walk on a treadmill at the rate of 2.6 miles per hour before and after their reduction in weight by a diet of 1375 calories daily. The increase in metabolism involved in moving one kilogram of body weight in a horizontal direction was tested. The results were very variable. Of eleven subjects tested after the 3 week period of undernutrition, four showed an increase in metabolism per horizontal kilogrammeter of body movement, one no change, and six a decrease from the level found when the men were living on a normal diet. Averaging the whole material, Benedict finds that the men after reduction can propel a kilogram of body weight one meter horizontally at an average expenditure of energy which is less by 6 per cent than was necessary to effect the same amount of work in the state of normal nutrition.

This does not accord with the results obtained by Joffe, Poulton and Ryffel (28), who compared the efficiency of an under-nourished individual, the basal metabolism of whom was only 26.6 calories per square meter of body surface per hour (Du Bois formula) instead of the normal of 40 calories, with the efficiency of a normally nourished person. The individuals walked at rates varying between 3 to 5 miles an hour. It was concluded that when the individual is not fatigued, prolonged undernutrition causes no alteration in the efficiency with which muscular work is carried out. The energy equivalent necessary to propel 1 kgm. 1 meter horizontally is the same in the state of undernutrition as in the state of normal nutrition. This accords with the experiments of Anderson and Lusk on the dog (see p. 542)

No experiments have been made to test the capacity of endurance in such men as Benedict investigated. It would be interesting to have men ride stationary bicycle ergometers until they were exhausted, *a*, before reduction, *b*, after reduction on an insufficient diet, *c*, after reduction on a sufficient diet.

The general physical reaction of the men to undernutrition Benedict described as follows:

1. Feelings of general weakness and tiredness, a condition commonly expressed in college slang as lack of "pep" or drive, when it seemed to require more energy to accomplish a given amount of work and it was necessary to urge one's self harder.
2. Weakness of the legs and accompanying unpleasant sensations of fatigue, particularly in stair-climbing.
3. Subnormal gymnasium and athletic performance, as shown by inability to continue the rapid calisthenics or to do the heavy apparatus work for the prescribed time and with the usual subjective satisfaction and generally to produce effectively sudden bursts of energy.

I have been informed by one who was a constant and expert witness of the gymnasium performances of these men that they could be readily differentiated from their fellows by their distinct lack of physical power. After the restricted diet the men ate food in enormous quantities and rapidly regained their original weights. No experiments upon their physical power immediately upon return to an adequate diet were made. It would be very important to determine if, given adequate food fuel to sustain prolonged muscular effort, men who had been moderately reduced in weight as were these subjects of Benedict would not have been equally powerful physically after reduction as they had been prior to the period of undernutrition. Rubner (49), however,

affirms that an increase in efficiency after undernutrition is to be observed only in those who were formerly over weight.

In work upon a dog Anderson and Lusk (2) found that the quantity of energy required to accomplish a given amount of work was the same whether the dog was in the best nutritive condition or had lost 20 per cent in weight after 13 days of fasting. The dog moved horizontally on a treadmill at the rate of 3 miles (4800 meters) per hour, and when well nourished accomplished this work at the expense of an extra energy production of 0.580 kilogrammeter per kilogram of body weight transported 1 meter, whereas after 13 days of fasting an energy equivalent of 0.584 kilogrammeter was required to accomplish the same unit of work. By reduction of the body weight, therefore, it was concluded that one may economize in the quantity of basal metabolism, one may economize in the quantity of food fuel required to move the lesser body weight, but if a given amount of work is to be done it can be accomplished only at the expense of a definite quantity of energy, irrespective of the body weight. The very constant results obtained with this well-trained dog are in marked contrast with the extremely varying results obtained subsequently by Benedict (see p. 540) upon men before and after reduction of their body weights, but they are in agreement with the findings of Joffe, Poulton and Ryffel. It should be remembered that dogs are often fasted for several days before they are run in a hunt, without any evident decrease in their muscular power.

Anatomical changes within the body. It has been noted by German authorities (50) that the loss of body fat causes a considerable displacement of the anatomical position of various organs of the body. In many a loss of subserous and mesenteric fat produced conditions in which the stomach and intestines were not as firmly held in position as formerly. A greater displacement of the heart and a ptosis of the stomach, intestines, kidney, uterus and vagina were observed. Cases of rupture and intestinal obstruction were commonly reported (9). Accompanying the general atrophy in human beings caused by inanition Kreger (34) describes a great diminution in the weight of the spleen, liver, pancreas, heart, testis, thyroid and kidney, while the brain and adrenal lose little or no weight.

Chemical changes within the body. When body fat is oxidized it is often replaced in the body by the addition of water, as has been shown by Grafe (18) in cases of obesity. Schirmer (52) finds that the fatty tissue of lean people is richer in water and connective tissue than is that of fat people. The muscles of thin people also contain more water than do those of fat people.

Schirmer likewise finds that the fat derived from the muscles of corpulent people has a higher iodine number and inferentially contains more oleic acid than does the fat found in the muscles of thin people.

The chemical composition of the protein composing the muscle of a dog appears to be independent of diet, whether rice or meat be fed, or of the nutritive condition of the animal. Diesselhorst (10) found in one dog that a sample of the dog's muscle showed that the C : N ratio of the protein content (what remains after extracting with water and ether) was 1 : 3.188 during fasting and 3.185 after taking a mixed diet. One would hardly expect that the chemical constitution of living protein would change in its essential constitution, only that its quantity in the cell might vary.

The influence of external cold. All authorities are united in the belief that the undernourished organism is far more susceptible to the sensation of cold than is the well-nourished. Protein, the most costly of the food-stuffs, causes a specific stimulus which increases the heat production, and carbohydrate and fat, when absorbed in excess of the immediate requirements of the body, both cause an additional heat production. In the well-nourished body these factors are protective against the sensation of cold. In the undernourished body, not only is the heat production reduced per kilogram and per square meter of surface, but the lack of protein and of an excess of calories in the food supply reduces to a minimum the extra production of heat following the ingestion of food. The body would then naturally react to conserve its heat resources by vasoconstriction of the superficial arterioles, which would leave the skin cold and therefore the temperature receiving sense organs especially sensitive to cold.

It is quite probable, though not definitely ascertained, that the phenomenon of increased heat production in the presence of cold (the chemical regulation of body temperature) would be accentuated in the presence of undernutrition, thereby becoming an important element in the reduction of the quantity of available body fat. The outcast who has suffered from hunger and cold is not in fit condition to saw wood.

The heart and circulation. Undernutrition reduces the number of heart beats per minute. Rubner (50) states that in the emaciated there is a slowing of the heart rate to 60, 50 or even to 40 per minute. The work to be accomplished by the circulation is certainly not as great as formerly. Determan (9) concludes that this reduction of the burden upon the heart and the blood vessels must be beneficial in heart disease and especially in arteriosclerosis.

In an elaborate study by Benedict and his associates of the pulse rate of men who had been reduced by partaking of a diet containing 1375 available calories daily for 3 weeks, a considerable number of them showed pulse rates reduced from a normal average of 56 to an average of 40 beats per minute. The records were taken early in the morning when the men were still in bed. The rate is as low as was observed in war edema in Germany. Electrocardiograms of these hearts showed normal conditions. There appeared to be no change in the functional efficiency of the heart; the reduction of rate was merely an accommodation to the lessened requirements of circulation. There was the usual adaptive increase in rate when additional work was called for. The blood pressure was reduced. The average systolic pressure fell from 120 mm. to 94 mm. and the diastolic from 83 mm. to 64 mm. The pulse pressure was therefore diminished from 37 mm. to 30 mm.

The influence of sex. German writers are generally agreed that the war diet tended to produce a cessation of the menses. Rubner (50) thinks that this complex undoubtedly depends upon the great reduction in the protein content of the diet. As this latter factor approaches the nitrogen minimum or falls below it, amenorrhea sets in as a protective factor. A great reduction of body weight is not essential. Eckstein (12) says that reports of this difficulty show that sometimes as high as 6 per cent of the women concerned in an investigation might be affected, so the trouble was by no means general. The cessation of the menses lasted between 2 to 18 months.

The development of the ovum and the ability to nurse the offspring were not reduced (53). Likewise the chemical composition of the mothers' milk was unchanged (44), though its quantity might be reduced. During 1916-17 the death rate among infants was below normal because mothers in increased numbers suckled their offspring. All this confirms the biological principle of the sacrifice of the mother for the welfare of the offspring.

Many German writers, as also Benedict, report that a reduced diet diminishes the *libido sexualis* among men.

War Edema. The occurrence of edema during a famine in France following the Napoleonic wars has already been described. The same phenomenon occurred in different localities in Europe during the World War. Rössle (48) states that in Bohemia in the year 1917, 22842 cases were reported, of whom 1028 died. Nine per cent of the inhabitants of one small town were afflicted with the disease.

The condition of edema occurs after chronic inanition extending over months and years and upon a diet containing predominantly carbohydrate and little protein. Schiff (51) states that he has occasionally seen apparently well-nourished individuals with this disease. A carbohydrate diet tends to favor an accumulation of water in the tissues. The occurrence of the trouble was widespread, especially in the cities, and occurred predominantly in the early part of 1917 when turnips replaced potatoes in the dietary. The older men, 40 to 55 years old, were especially affected, younger people and women much less. There was a swelling of legs, arms, and sometimes of other parts, but no pathological changes in kidney, heart, or liver, nor was there any other severe organic lesion. There was bodily weakness, slow pulse (40 to 48), a reduction in the volume of the blood, polyuria (3 to 4 liters), blood hydremia and sometimes nervous symptoms. Rest in bed and better food—more fat, milk, meat and bread—usually effected a cure. The mortality rate was not high.

Rubner (50) has never noticed this condition in fasting dogs, and concludes that the acute road of starvation yields a sufficient amount of protein metabolism, and this he considers to be the essential factor in preventing the edema. The functional disturbances may be very severe and often do not disappear with the regression of the edema, while weakness and emaciation, slow pulse, and frequent urination may persist for a long time after again taking a normal diet. Even the best treatment does not always prevent a fatal outcome, though autopsy may show no organic lesion. There is in general a regression of the disturbance when fresh foods are obtainable from a new harvest.

Those who have been cured by dieting are susceptible to a recurrence of the disease if the poor diet is again taken.

Knack and Neumann (30) found a reduced quantity of lipoids in the blood of patients suffering from edema. They think that this reduction of lipoids may cause damage to the capillaries and to the cell walls, thus increasing the permeability of both. After administering carbohydrate alone in the form of turnips, or excess of water alone, to a patient who had recovered from edema, there was no recurrence of the difficulty, but when both were administered together edema followed.

Harden and Zilva (20) gave to a monkey 250 to 300 grams of polished rice daily, with a yeast preparation to furnish the water soluble vitamine, prepared lemon juice to furnish the antiscorbutic vitamine, and a salt mixture. The experiment began on May 16, 1918. A decline

in body weight began the end of January. Edema developed on February 27, 1919, 289 days after commencing the experiment. The edema persisted and grew gradually worse, a severe diarrhea set in, and the animal was chloroformed on account of its suffering.

Falta and Quittner (13) believe that the edema is due to the large amount of chloride ingested in the food and is analogous to diabetic edema following the ingestion of sodium bicarbonate together with a diet rich in salt. The day's urine, which is always free from albumin, may contain 40 to 45 grams of sodium chloride.

In some excellent studies upon rats Kolman (31) was able to produce edema in them by giving a diet composed largely of carrots with carrots as the only source of protein. Fats or fat or water-soluble vitamins did not prevent the occurrence of the edema in these rats living on a low protein diet. The salt content of the diet had no noticeable effect. A large water intake favored the development of the trouble. Control rats received casein as an addition to the diet, and remained in good health. Hence, the carrots did not contain "toxic" substances. This research confirms the opinion of Rubner that a diet low in protein produces edema.

Maver (40), reviewing the literature of nutritional edema, finds no indication that a lack of vitamins is concerned in its production.

Rubner (50) notes that *polyuria* was extensively observed in 1917 and is to be explained by the enormous water content of the diet for on account of a lack of fat the food intake consisted of bread, turnips, vegetables, potatoes and soup preparations. It was noticeable that urinary secretion took place, especially during the night hours, and bed-wetting was of frequent occurrence, even in adults. This was due to a delayed absorption of food, a more profound sleep in weakened individuals, to the absence of urea and the purins, and of tea and coffee as diuretic agents.

Metabolism of atrophic children. The same problems of energy production are met with in undernourished children as in the cases of adults. Howland (23), (24) investigated the metabolism of two normal infants (I and II); also the metabolism of a boy (III) 6 months old who was in a condition of extreme malnutrition, was literally skin and bones, with no fat and very little musculature; and finally the metabolism of an 8 year old girl (IV) emaciated to a most extreme degree and almost devoid of musculature. She had suffered from cerebrospinal meningitis $6\frac{1}{2}$ years before.

The energy metabolism of these children may thus be given:

Heat production in normal and undernourished children

	CONDITION	AGE	WEIGHT	CALORIES IN 24 HOURS				PER KILO- GRAM
				Indirect	Direct	Per square meter surface		
						Indirect	Direct	
			kgm.					
Child I.....	Normal	3 mos.	4.65	340	333	1084	1046	71.3
Child II.....	Normal	7 mos.	4.32	358		1270		83.0
Child III.....	Malnutrition	6 mos.	3.05	188	191	868	886	62.0
Child IV.....	Atrophic	8 yrs.	6.60	293		809		44.4

The children were all nourished with milk, and the determinations were made when they were asleep after food ingestion. Howland's formula (24) for determining the surface area of children was employed. Using this formula, the results are usually not far from those obtained by using that of Lissauer.

It appears from the above table that the metabolism of atrophic children is less per kilogram of body substance and per square meter of surface than in normal children.

It is to be greatly regretted that no work similar to this has yet been published concerning the metabolism of undernourished children in Vienna.

Von Pirquet's (47) system of nutrition, which need not here be analyzed, seems to have given excellent practical results in the nutrition of the underfed Viennese children. Concerning this system von Leersum concludes, "plus que ça change, plus c'est la même chose." Fleming (14) states that only when children are one-third under weight for their ages is the metabolism abnormally decreased.

Xerophthalmia. McCollum and Davis (38) and, independently and almost at the same time, Osborne and Mendel (45) found that if rats were reared upon a synthetic diet which included lard or a vegetable fat the animals, after about 2 months, ceased to grow and became afflicted with an inflammation of the eyes, xerophthalmia. Osborne and Mendel (46) noted the great efficacy of cod liver oil as a cure for this condition. Xerophthalmia has been more common in Denmark than elsewhere, probably because the poor there eat vegetable margarine and export Danish butter. In 1917, during the submarine blockade, the prevailing doctrine in Denmark was that of Hindhede to the effect that fat was a dispensable foodstuff, an error also cham-

pioned by von Pirquet (47A). There was then no knowledge in Denmark of the American work. Bloch (5) (6) describes how the Danish children grew to be weaklings, without appetite, under height and under weight for their ages, and they developed xerophthalmia. These conditions were cured by rationing butter and selling it to the poor at low prices. Administration of full milk and cod liver oil were also effective. Ten grams of cod liver oil, given twice daily, cured the xerophthalmia in 8 days except in cases in which its administration had been too long delayed to save the eyesight.

One can hardly cite a more clear-cut example of the benefits conferred upon a people from knowledge of experimental biological science.

It is not within the scope of this review to deal with the deficiency diseases, scurvy, beri-beri, pellagra and rickets, concerning each one of which volumes have already been written, and each one of which is worthy of separate consideration.

Undernutrition and the incidence of disease. With the loss in weight it was particularly noted in Germany that there was an increased frequency of tuberculosis until, at the end of the war, the death rate from this disease had doubled or had reached the height which it had formerly attained before modern control over its spread has been instituted. More new cases were also enumerated. Young children were more susceptible to it than formerly. The increased susceptibility to cold likewise increased the number of cases of pulmonary infections. There was a great loss by death of people over 60 years old. Bodily weakness especially threatens people of old age, who may live for many years when amply nourished, but when undernourished, succumb to an ordinarily unimportant bronchitis, catarrh of the stomach, or to an acute infection (9). Recovery after surgical operations was also more difficult. On the contrary, war nutrition, by diminishing the intake of protein and preventing over-nutrition, was beneficial to many diabetic patients (43). The reduction in the quantity of alcohol taken was of benefit in all countries. In general, the gastro-intestinal tract showed itself capable of adaptation to the war diet to a very high degree (9).

The prevention of famine. From what has preceded it is evident that sufficient food is essential for the physical, mental and moral welfare of a nation, and it therefore follows that human intelligence should be used for the prevention of famine. The doctrines of T. B. Wood (55) became the recognized English agricultural policy during the war. Gruber (19) has outlined a similar policy for adoption by the German people in the light of their situation in 1920. The reasoning is funda-

mentally sound. He begins by unrolling a hopeless picture of the food situation. As the possibilities of emigration are limited, twenty millions Germans are condemned to die unless they are able to help themselves. People in their position cannot speak of "panis et circenses" but of "panis et labor." The only outcome possible is to nourish themselves from their own land and render themselves independent of foreign imports. Notwithstanding the dark prospect, Gruber believes it possible to maintain nourishment from home produce if there be no extravagance and especially if the protein intake contain only a small quantity of meat. The ox is an irrational utilizer of fodder; if too many cattle are maintained an irreplaceable quantity of fodder is wasted. Agriculture must react to accord with this. The population needs 2600 calories per person per day, or for 60,000,000 people 56 billion calories per annum. Notwithstanding the loss of agricultural districts, 171 billion calories can be produced as food for men and beasts. Of this, 26 billion are needed for horses, leaving 145 billion over for man and for edible animals. Because of the poor utilization of fodder by animals, not more than 29 per cent of the food of man should consist of milk, meat and eggs (which the fodder available could supply), whereas 71 per cent should come from vegetables. It is necessary for agriculture to appreciate its high patriotic obligation not to increase the number of cattle nor to neglect the tilled area. Of course, this is not to be accomplished by force. It must be done by explaining the situation. Gruber protests against the brewing of strong beer and against the export of native grain. The nutrition question depends upon the sense of responsibility of each individual, producer and consumer alike. The problem is not only psychical but a matter of habit and of will power. "The German people holds the fate of Europe in its hand. With starvation, anarchy will come; anarchy in Germany would mean the end of European culture."

Hindhede (21) writes: "The (German) people must first have bread, potatoes and cabbage in sufficient quantity and then some milk. Meat is the last requirement to be met. If the people must wait until the pigs and cattle have sufficient food, they will die of starvation one year before they can get an abundance of meat."

During the last year of the war E. H. Starling said vehemently in England: "We will not ration bread." The necessary calories were thereby assured. And Herbert Hoover has written, "The wheat loaf has ascended in the imagination of enormous populations as the positive symbol of national survival."

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ANIMAL CALORIMETRY.

SEVENTEENTH PAPER.

THE INFLUENCE OF COLLOIDAL IRON ON THE BASAL METABOLISM.

By EINAR LANGFELDT.

Christiania, Norway.

*(From the Physiological Laboratory of Cornell University Medical College,
New York City.)*

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INTRODUCTION.

The biological action of inorganic hydrosols has been extensively studied during the years which have elapsed since Credé¹ introduced the use of colloidal silver into medicine. From these investigations it seems very probable that the action of the inorganic hydrosols is much the same as the action of small doses of salts of the same metals (see the literature by Bechhold²).

The colloidal metal dissociates slowly in water into metal ions, and the bactericidal action, the property which has been the most studied, is supposed to be due to these dissociated ions. After intravenous injection the colloids are distributed all over the body within $\frac{1}{2}$ to 1 hour and, while still in the colloidal state, are deposited in almost every organ with subsequent slow dissociation of ions.

Investigations on the influence of these substances upon the metabolism are very rare. It has been found that silver hydrosol increases the protein metabolism.³

A special interest is connected with the negative iron oxide hydrosol. While the positive iron oxide hydrosol, according to

¹ Credé, B., *Arch. klin. Chir.*, 1897, lv, 861.

² Bechhold, H., *Die Kolloide in Biologie und Medizin*, Dresden and Leipsic, 2nd edition, 1919.

³ Bechhold,² p. 402.

Bechhold, unites with the negative blood colloids, forming an irreversible gel, the negative iron oxide hydrosol easily mixes with serum without producing any coagulation. This colloid solution is said to act as an oxygen carrier and to have properties similar to hemoglobin.⁴

The purpose of this investigation has been to examine the influence of such an intravenously injected colloidal iron solution on the basal metabolism.

Methods.

Two dogs, trained for calorimeter work, were used in the experiments. The dogs were fed once daily with the "standard diet."⁵

The bladder was emptied and washed before and after each experiment.

The hydrosol was injected into the jugular vein, and immediately thereafter the dog was placed in the calorimeter. In each experiment 5 cc.⁶ were used.

The movements of the dog in the calorimeter were recorded on a smoked drum.

The efficiency of the calorimeter was controlled by frequent alcohol checks.

Basal Metabolism.

The standard diet was administered at 5 p. m. the day before the experiment. Thus, the basal metabolism was determined 18 to 20 hours after feeding.

In all experiments the dog was perfectly quiet, and the temperature of the calorimeter was between 25 and 26°C.

The basal metabolism of Dog 20 was found to average 14.92 calories per hour and the respiratory quotient 0.80 (Table I).

The basal metabolism of Dog 18 was found to be 16.18 calories per hour and the respiratory quotient 0.80.

The Influence of Colloidal Iron Intravenously.

The results of intravenous injection of 5 cc. of colloidal iron are given in Table II. The average total heat production per hour

⁴ Bechhold,³ p. 417.

⁵ Lusk, G., *J. Biol. Chem.*, 1912-13, xiii, 185.

⁶ Made by Laboratoires Clin, Paris.

of Dog 20 was 16.00 calories and the average respiratory quotient 0.84. One of the experiments, No. 10-A, was performed immediately after the basal metabolism was determined, on the same day.

After administering colloidal iron the heat production of Dog 18 was found to be 18.72 calories per hour and the respiratory quotient 0.82.

TABLE I.
Basal Metabolism of Dog 20.

Date.	Experiment No.	Indirect calorimetry.	R. Q.
<i>1921</i>			
Apr. 7.....	3	14.45	0.81
May 6.....	5	14.77	0.79
" 9.....	7	14.94	0.81
" 13.....	10	15.25	0.78
" 14.....	11	15.22	0.81
Average		14.92	0.80

TABLE II.
Colloidal Iron Intravenously—Dog 20.

Date.	Experiment No.	Indirect calorimetry.	R. Q.
<i>1921</i>			
Apr. 8.....	4	15.63	0.85
May 7.....	6	15.79	0.87
" 13.....	10-A	16.40	0.81
Average		16.00	0.84

The total heat production was thus increased about 7 per cent in Dog 20 and about 15 per cent in Dog 18.

The average CO₂ output per hour of Dog 20 after the injection was 5.51 gm., but only 4.89 gm. in the basal metabolism. The average O₂ consumption was 4.68 gm. per hour after injection and 4.46 gm. in the basal metabolism.

In Dog 18 the CO₂ production was increased from 5.37 to 6.35 gm. per hour and the O₂ consumption from 4.87 to 5.63 gm. per hour after the injection.

TABLE III.
Dog 20.
Standard diet given at 5 p.m. the previous day. The results are expressed in average values per hour.

Date.	Experiment No.	Time.	CO ₂	O ₂	R. Q.	H ₂ O	Urine N.	Calories.			Remarks.
								Protein.	Non-protein.	Total heat calculated.	
1921 Apr. 7	3 Basal.	11.22-2.22	gm. 4.80	gm. 4.33	0.81	gm. 11.06	gm. 0.082	2.18	12.27	14.45	Alcohol check Apr. 4, average R. Q. 0.665. Weight 8.47 kg. Dog quiet.
"	4 Colloidal iron intravenously.	11.32-2.32	5.52	4.65	0.85	12.86	0.095	2.52	13.11	15.63	Weight 8.47 kg. Colloidal iron intravenously, 5 cc. Dog quiet.
May 6	5 Basal.	11.18-2.18	4.77	4.40	0.79	12.15	0.098	2.62	12.15	14.77	Alcohol check May 5, average R. Q. 0.667. Weight 9.20 kg. Dog quiet.
"	6 Colloidal iron intravenously.	11.57-1.57	5.58	4.47	0.87	11.47	0.105	2.80	12.99	15.79	Weight 9.10 kg. Colloidal iron intravenously, 5 cc. Dog quiet.
"	7 Basal.	12.02-2.02	4.92	4.39	0.81	11.12	0.098	2.60	12.34	14.94	Weight 9.10 kg. Dog quiet.

May 13	10 Basal.	11.10- 1.10	4.91	4.60	0.78	15.43	0.071	1.90	13.35	15.25	Alcohol check May 10, average R. Q. 0.638. Weight 9.30 kg. Dog quiet.
" 13	10-A Colloidal iron intravenously.	2.40- 5.40	5.43	4.92	0.81	12.96	0.077	2.03	14.38	16.40	5 cc. colloidal iron intravenously 20 min. after the last experiment. Between these experiments the dog was catheterized, but received no food or drink. Dog quiet.
" 14	11 Basal.	10.25-12.25	5.04	4.57	0.81	11.32	0.079	2.09	13.13	15.22	Weight 9.20 kg. Dog quiet.

TABLE IV.
Dog 18.

Standard diet given at 5 p.m. the previous day. The results are expressed in average values per hour.

Date.	Experiment No.	Time.	CO ₂	O ₂	R. Q.	H ₂ O	Urine N.	Calories.			Remarks.
								Protein.	Non-protein.	Total heat calculated.	
1921 May 17	85 Basal.	12.25-2.25	gm. 5.37	gm. 4.87	0.80	gm. 7.86	gm. 0.107	2.85	13.33	16.18	Weight 9.45 kg. Dog quiet.
" 18	86 Colloidal iron intravenously.	11.36-1.36	gm. 6.35	gm. 5.63	0.82	12.37	0.137	3.65	15.07	18.72	Colloidal iron intravenously, 5 cc. Weight 9.45 kg. Dog quiet.

The respiratory quotient was slightly higher in both dogs during the injection experiments than during the determinations of the basal metabolism.

There was no marked increase of the protein metabolism. The chief increase of the total heat production fell on the non-protein metabolism.

The results are summarized in Tables III and IV.

CONCLUSIONS.

1. Intravenous injections of iron hydrosol in dogs cause an increase of the O_2 consumption and the CO_2 production. The average increase of the heat production in one of these dogs was 7 per cent and in one experiment on the other the increase was 15 per cent.

2. The increased metabolism coincides with a slight increase of the respiratory quotient.

3. The chief increase of the total heat production falls on the non-protein metabolism.

I wish to express my sincerest thanks to Professor Graham Lusk for advice and help in running the calorimeter, and to Mr. James Evenden for technical assistance.

ANIMAL CALORIMETRY.

EIGHTEENTH PAPER.

THE BEHAVIOR OF VARIOUS INTERMEDIARY METABOLITES UPON THE HEAT PRODUCTION.*

By GRAHAM LUSK.

WITH THE TECHNICAL ASSISTANCE OF JAMES EVENDEN.

(From the Physiological Laboratory of Cornell University Medical College,
New York City.)

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I. INTRODUCTION.

The behavior of the ordinary foodstuffs during successive hours after their ingestion as they react in the organism of the dog has been the subject of numerous former researches published from this laboratory. The last paper upon this theme was issued in 1919 (1) and dealt with the similarity of the extent of the rise in heat production after giving lactic acid and alanine. It was then

*An abstract of this paper was presented before the Physiological Congress held in Paris, July, 1920.

(erroneously) concluded that the ingestion of the two substances resulted in the same physiological reaction upon metabolism.

In 1912 the writer (2) proved that glycine and alanine were powerful stimuli to increased heat production. At the same time Benedict (3) advanced the theory that the specific dynamic action of the foodstuffs was due to stimuli arising from the formation of organic acids. This has been elsewhere discussed by me (4).

In the light of our present knowledge it seemed desirable to investigate the comparative behavior of various simple substances, such as acetic, glycollic, lactic, and hydrochloric acids; the behavior of glycine after neutralization with sodium bicarbonate, of sodium lactate and sodium glycollate, and of sodium bicarbonate itself. In this manner one might discover to what extent the acidic radicle was a dominant factor influencing metabolism. Since strong solutions of acetic acid were vomited by the dog, one could administer only small quantities to the animal. As noted in the previous paper, it was found possible to administer materials like lactic acid in a solution containing 2.5 gm. of Liebig's extract of beef warmed to a temperature of 38°C. For the reason of the presence of Liebig's extract in the diet, the protein metabolism throughout the whole series of experiments was estimated on the basis of a urinary nitrogen elimination of 0.132 gm. per hour, as was determined for the basal metabolism of the dog employed. The figures given represent in general the measurements of the metabolism obtained during the 2nd and 3rd hours after administering the substances. The results obtained in this paper should be considered in the light of the paper by Miss Taistra (5) which follows this.

II. THE BASAL METABOLISM.

A dog was given the "standard diet" (6) at 5 p.m. the day before the experiment and also regularly throughout the entire period of experimentation. The basal metabolism was determined about 18 hours after the ingestion of this maintenance diet. The results are summarized in Table I.

According to these determinations the basal metabolism by indirect calorimetry averages **17.61** calories per hour and the respiratory quotient **0.80**.

TABLE I.
Basal Metabolism of Dog XIX.

Experiment No.	Date.	Duration of experiment.	R. Q.	Calories.		
				Indirect.	Direct.	Difference.
	1920	hrs.				
6	Jan. 15	2	0.82	35.59	37.54	+1.95
19	Feb. 5	2	0.84	33.12	33.52	+0.40
24	Mar. 16	2	0.80	35.37	31.30	-4.05
29	" 30	2	0.76	36.59	36.14	-0.45
32	Apr. 6	2	0.75	36.52	35.78	-0.74
35	" 12	2	0.79	34.75	34.80	+0.05
38	" 21	1	0.81	16.90	16.75	-0.15
Total..		13	0.80	228.84	225.83	-3.01 = 1.3 per cent

III. LIEBIG'S EXTRACT OF BEEF.

The influence of 2.5 gm. of this material, when given with 500 cc. of water to Dog XVIII, was found to increase the basal metabolism by 1.1 and 0.8 calories per hour, as has already been described by Atkinson and Lusk (1). In the present instance the administration of 2.5 gm. of the substance in a smaller quantity of water, 400 cc., caused a scarcely appreciable rise in heat production above the basal level. The experiments may be thus expressed:

TABLE II.
Metabolism of Dog XIX after Administering a Broth Containing 2.5 Gm. of Liebig's Extract of Beef.

Experiment No.	Date.	Volume of the broth.	Duration of experiment.	R. Q.	Calories per hour.		
					Indirect.	Direct.	Difference.
	1920	cc.	hrs.				
7	Jan. 16	350	2	0.79	36.53	34.38	-2.15
14	" 28	400	2	0.81	38.93	43.41	+4.48
21	Feb. 9	400	1	0.82	19.79	19.99	+0.20
23	" 19	400	2	0.81	34.25	37.10	+2.85
25	Mar. 19	400	2	0.80	34.72	34.06	-0.66
34	Apr. 9	400	2	0.82	33.91	33.22	-0.69
Total..			11	0.81	198.13	202.16	+4.03 = 2.0 per cent

The average heat production, as determined by indirect calorimetry after giving 400 cc. of a broth containing 2.5 gm. of meat extract, was 18.1 calories per hour, or 0.49 calory above the basal metabolism. The difference is so slight as to be negligible. The average respiratory quotient 0.81 is essentially the same as that of the basal metabolism.

IV. SODIUM BICARBONATE.

In order to detect the influence of sodium bicarbonate, 8 gm. of the material were ingested with 300 cc. of water and 2.5 gm. of Liebig's extract, with the following experimental results:

TABLE III.

Dog XIX after Administering a Broth Containing 8 Gm. of NaHCO_3 , 2.5 Gm. of Liebig's Extract, and 300 Cc. of Water.

Experiment No.	Date.	Duration of experiment.	R. Q.	Calories per hour.		
				Indirect.	Direct.	Difference.
	1920	Hrs.				
42	May 1	2	0.84	37.22	37.58	+0.36
43	" 4	1	0.82	16.95	17.72	+0.77
Total....		3	0.83	54.17	55.30	+1.13 = 2.1 per cent

The rate of metabolism averages here 18.05 calories per hour, an increase of 0.45 above the basal metabolism, about the same as when the broth alone was given. The increase may be considered negligible.

V. ACETIC ACID.

The behavior of acetic acid is of especial interest in that it is probably a cleavage product of fatty acid as a consequence of its β -oxidation. Acetic acid on combustion manifests a respiratory quotient of 1.00 and 1 gm. of the substance requires 1.067 gm. of oxygen and yields 3.491 calories of heat. One may calculate that 1 liter of oxygen thus employed would correspond to the formation of 4.674 calories. This is essentially the same value for oxygen as when a liter of it oxidizes fat and produces 4.686 calories with the respiratory quotient 0.71.

The following results were obtained in the dog after ingesting 3 gm. of acetic acid:

TABLE IV.

Dog XIX after Administering 3 Gm. of Acetic Acid in Broth Containing 8.5 Gm. of Liebig's Extract of Beef and 400 Cc. of Water.

Experiment No.	Date.	Duration of experiment.	R. Q.	Calories per hour.		
				Indirect.	Direct.	Difference.
	1880	hrs.				
4	Jan. 12	2	0.76	42.55	42.52	-0.03
12	" 23	2	0.79	41.25	42.77	+1.52
13	" 27	2	0.78	40.63	38.33	-2.30
Total...		6	0.78	124.43	123.62	-0.81 = 0.6 per cent

This indicates that the metabolism of the dog, following the ingestion of 3 gm. of acetic acid containing 10.5 calories, rises to an average of 20.74 calories per hour, an increase of 3.13 calories above the basal level.

An unusual phase of this work is the presence of a low respiratory quotient following the ingestion of a material having a high quotient. Curiously enough, the same phenomenon of a reduced respiratory quotient appeared also when glucose and acetic acid were given together.

The experiments are all calculated without reference to the special modifications induced through the combustion of acetic acid. If, however, one recalculates the 1st hour of Experiment 12, in which the respiratory quotient was 0.83, on the hypothesis that as large a quantity as 1 gm. of acetic acid was oxidized during that interval, then the non-protein respiratory quotient for fat plus carbohydrate would reach the artificial value of 0.68. On this basis the calories of metabolism would be derived as follows: protein 3.50, acetic acid 3.49, fat 12.72, total 19.71. This contrasts with a total of 20.30 calories determined by the usual mode of calculation, a diminution of 0.59 calory for the hour. The usual method of calculating the results cannot therefore be wide of the mark.

It is possible that acetic acid may in part have been reduced in the organism to ethyl alcohol, which would explain the low respiratory quotient obtained, but of this there is no actual evidence. The experimental evidence shows that administration of acetic acid does not reduce the carbon dioxide-combining power

of the blood, hence one may conclude that it is rapidly absorbed and oxidized (5).

In a former experiment (Experiment 30, Dog III (7)) the administration of 5.8 gm. of ethyl alcohol, which if oxidized to acetic acid would have given rise to 7.6 gm. of the latter substance, effected an increase in the basal metabolism of only 0.9 calory per hour. It is well known that alcohol is only slowly oxidized, whereas acetic acid appears to be rapidly consumed.

VI. LACTIC ACID.

Lactic acid is believed by many to be a normal intermediary metabolite of glucose (8-12) as well as of alanine. Its behavior in metabolism may therefore merit further investigation. Solutions of 4.8 gm. were given to Dog XIX with the following results:

TABLE V.

Dog XIX after Administering 4.8 Gm. of Lactic Acid in Broth Containing 2.5 Gm. of Liebig's Extract and 400 Cc. of Water.

Experiment No.	Date.	Duration of experiment.	R. Q.	Calories per hour.		
				Indirect.	Direct.	Difference.
	1920	hrs.				
10	Jan. 21	2	0.83	39.91	38.70	-1.21
11	" 22	2	0.84	41.14	40.34	-0.80
Total....		4	0.84	81.05	79.04	-2.01 = 2.5 per cent

Lactic acid, 4.8 gm., brought the rate of heat production to 20.26 calories per hour, an increase above the basal metabolism of 2.65 calories. The respiratory quotient of 0.84 is slightly higher than the average basal value of 0.80, in conformity with the fact that the respiratory quotient of lactic acid is 1.00.

The administration of lactic acid in this quantity temporarily reduced the CO₂-combining power of the plasma of this dog (5) and yet the increase in the heat production was less than was observed in the case of acetic acid administration where no reduction was observed.

To determine whether the administration of lactic acid in the form of an alkaline salt would abolish its specific dynamic influence, 10 gm. of sodium lactate were given, with the following results:

TABLE VI.

Dog XIX after Giving 10 Gm. of Sodium Lactate in Broth Containing 2.5 Gm. of Liebig's Extract and 400 Cc. of Water.

Experiment No.	Date.	Duration of experiment.	R. Q.	Calories per hour.		
				Indirect.	Direct.	Difference.
	1880	hrs.				
33	Apr. 8	2	0.82	38.11	36.29	-1.82
36	" 13	2	0.81	37.99	36.42	-1.57
Total...		4	0.82	76.10	72.71	-3.39 = 4.5 per cent

By the indirect method the heat production is 19.02 calories per hour; an increase of 1.41 calories above the basal. The respiratory quotient is that usually found. The urine eliminated at the end of the experiments was weakly alkaline to litmus.

If the sodium lactate were oxidized to NaHCO_3 , the chemical reaction would be $\text{C}_3\text{H}_5\text{O}_2\text{Na} + 3\text{O}_2 = \text{NaHCO}_3 + 2\text{CO}_2 + 2\text{H}_2\text{O}$. Under these circumstances the respiratory quotient would be 0.667 and the quantity of oxygen absorbed the same as would be required to oxidize lactic acid itself. Since the respiratory quotient actually found is 0.82, it is evident that the alkali could not have been entirely, or even largely, neutralized by carbonic acid.

The increase of 1.4 calories caused by 8 gm. of lactic acid administered as a sodium salt is not as great as that of 2.7 calories when only 4.6 gm. were given in the form of the free acid. This might be due to the fact that the presence of alkali promotes the conversion of lactic acid into glycogen. It should be recalled that the ingestion by a dog of 8 gm. of glucose into which 8 gm. of lactic acid are convertible has no effect whatever upon the metabolism (1). The intermediary metabolite is therefore more immediately available for use by the cell than is glucose which may be at once dehydrated and put aside as glycogen. To some this may appear to favor the theory that glucose must become glycogen before it can be utilized.

VII. GLYCOLLIC ACID.

Glycollic acid has been suggested as the primary product following the deamination of glycine. As such it might be the cause of the profound stimulation of metabolism which follows the administration of glycine itself. The literature concerning the intermediary metabolism of glycollic acid is given by Sieburg and Vietense (13). Pohl (14) could find neither glycollic nor oxalic acid in the urine of a dog to which he had given the substance. Mayer (15), however, gave 10 gm. of glycol to a rabbit and recovered one-sixth of it in the form of glycollic acid in the animal's urine. Dakin (16) noted a rise in urinary ammonia from 0.12 to 0.22 gm. per day after giving 1.1 gm. of glycollic acid to a dog weighing 11 kilos.

In combustion glycollic acid manifests a respiratory quotient of 1.33. When 1 gm. is oxidized 0.632 gm. of oxygen is consumed and 2.206 calories are liberated. Each liter of oxygen employed has a value of 4.990 calories or approximately the same value as when glucose is oxidized.

Glycollic acid, 7.6 gm., containing about twice the number of potential H ions present in the quantities of acetic and lactic acids previously administered, were given to the dog and the results were as follows:

TABLE VII.

Dog XIX after Giving 7.6 Gm. of Glycollic Acid in Broth Containing 2.5 Gm. of Liebig's Extract and 400 Cc. of Water.

Experiment No.	Date.	Duration of experiment.	R. Q.	Calories.		
				Indirect.	Direct.	Difference.
	1920	hrs.				
20	Feb. 6	2	0.93	39.01	31.51	-7.50
22	" 18	2	0.96	37.33	36.01	-1.32
26	Mar. 20	2	0.91	38.27	34.14	-4.13
Total..		6	0.94	114.61	101.66	-12.95
37*	Apr. 20	3	0.88	55.47	50.91	-4.56

* Material given as a sodium salt.

The metabolism calculated by the indirect method is 19.10 calories per hour or an increase of 1.49 calories above the basal.

The high average respiratory quotient of 0.94 betokens the oxidation of the ingested material.

Administration of glycollic acid produced a profound fall in the CO_2 -combining power of the blood plasma (5), indicating that a considerable quantity of the salt combines with the alkali of the blood and circulates in it.

This reduction in CO_2 -combining power from 60 to 40 volumes per cent might have caused the elimination of 100 cc. of CO_2 from 500 cc. of blood presumably contained in the dog of 10 kilos body weight. Even though the whole of this elimination should have fallen upon the 2nd and 3rd hours recorded in the above experiments the increase in the respiratory quotient would have been only 0.02. Bicarbonate withdrawn from the tissues into the blood may have materially increased the CO_2 output.

The great reduction in the CO_2 -combining power of the blood, with only a slight increase in the total metabolism, indicates that acid metabolites, when ingested, do not necessarily stimulate metabolism because of their acid properties.

When glycollate of sodium was given to the dog the increase above the basal metabolism was 0.88 calory per hour. The respiratory quotient was 0.88, indicating the combustion of the substance. If the salt had been oxidized with the production of NaHCO_3 , its respiratory quotient would have been 0.80. The quotient obtained indicates that factors other than CO_2 for the neutralization of the alkali were brought into play.

An interesting phenomenon in relation to the ingestion of both glycollic acid and its salt is the reduced measured heat output of the dog despite the slightly increased heat production as computed from the oxidation process. This was also noticed when hydrochloric acid was ingested. It is evident, therefore, that heat was stored in the body which was not reflected by the rectal thermometer carried by the animal. There might have been an altered distribution of the blood supply so that some portion of the body attained an increased temperature. These experiments confirm the idea that for short periods the indirect method of heat production is usually more to be relied upon than the direct measurement.

VIII. HYDROCHLORIC ACID.

Atkinson and Lusk (17) demonstrated that the administration of 200 cc. of 0.4 per cent hydrochloric acid will increase the hourly heat production in the dog from 20 to 21.25 calories per hour, an increase of 1.25 calories.

In Experiment 28, 300 cc. of water containing 0.6 per cent of hydrochloric acid and 2.5 gm. of Liebig's extract were given to Dog XIX. The heat production as calculated was 19.16 calories per hour, an increase of 1.55 calories above the basal.

The experiments of Miss Taistra show that a considerable fall in the CO_2 -combining power of the blood takes place as the result of giving hydrochloric acid in this quantity to the dog. There is, however, no great rise of metabolism in consequence.

IX. SODIUM SALT OF GLYCINE.

Lusk (2) has shown that glycine is a powerful stimulant to metabolism. It might be that when administered as a sodium salt its active properties would disappear. Therefore, 9.55 gm. of the substance were dissolved in 300 cc. of water and neutralized by the addition of 10.7 gm. of bicarbonate of sodium. The calculations of metabolism followed the method given by Lusk (7) and the results may thus be summarized:

TABLE VIII.

Dog XIX after Giving 9.55 Gm. of Glycine in 300 Cc. of Water with 10.7 Gm. of NaHCO_3 and 2.5 Gm. of Liebig's Extract.

Experiment No.	Date.	Duration of experiment.	R. Q.	Calories.		
				Indirect.	Direct.	Difference.
	1920	hrs.				
39	Apr. 22	2	0.84	45.84	45.37*	-0.47

* During the 1st hour, the heat from evaporated water was estimated.

The heat production was 22.94 calories per hour, an increase of 5.31 calories above the basal. This accords with Experiment 61 on Dog III (7) in which administration of 10 gm. of glycine increased the metabolism 4.4 calories.

The specific dynamic effect of glycocoll is therefore in no way diminished by administering it with alkali and the result is far

greater than is achieved after giving the nearly equivalent quantity of 7.6 gm. of glycollic acid, supposedly formed from it by hydrolytic deamination.

These experiments, however, do not exclude the possibility that after all glycollic acid may be the stimulus which increases metabolism, for it has been known since the experiments of Folin and Denis (18) that ingested glycine is absorbed with avidity by the cells of the muscles and liver, and it may be that if deamination takes place within them with the production of glycollic acid, this substance may then play quite a different rôle from that which it plays when brought to the cell from without. Considerations of this sort show to what extent the experimental limitations of the method may play havoc with one's interpretation of the results obtained.

Dakin (19) suggests that glycine reacts upon other amino-acids capable of forming glucose (*e.g.*, alanine), setting them free in the body. These would then become the source of sugar following glycine ingestion and the source of its specific dynamic action. This harmonizes with the fact that 1 molecule of glycine has the same specific dynamic effect as a molecule of alanine, but if 1 molecule of glycine caused the liberation of a molecule of alanine in metabolism in the phlorhizinized dog, then more "extra glucose" would be eliminated than actually takes place.

X. GLUCOSE WITH AND WITHOUT LACTIC AND ACETIC ACIDS.

One of the peculiarities of the specific dynamic action of amino-acids, glucose, and fat is that the extra heat produced by one of the three is specific and that when two or more of the materials are given together the extra heat production is the sum of the influences which each substance given alone would have induced (7). In line with this knowledge it follows that if glucose and lactic acid be given together and lactic acid behaves like a metabolite of alanine, the heat production will be greater than when glucose alone is given, but if it behaves like a metabolite of glucose no appreciable rise will be observed. Also, if acetic acid be given with glucose, one can in like manner analyze whether acetic acid is a normal metabolite of glucose, as it might be if acetaldehyde, supposedly a cleavage product of glucose, were oxidized.

For this purpose the following solutions were given:

- A. Glucose, 58 gm. + water, 400 cc. + Liebig's extract, 2.5 gm.
 B. Glucose, 50 gm. + lactic acid, 8 gm. + water, 400 cc. + Liebig's extract, 2.5 gm.
 C. Glucose, 50 gm. + acetic acid, 3 gm. + water, 400 cc. + Liebig's extract, 2.5 gm.

It is evident from Table IX that there is no summation of effect when glucose and lactic acid are given together. Hence ingested lactic acid behaves like a metabolite of glucose and not like one of alanine.

TABLE IX.
Dog XIX after Giving Diets Above Mentioned.

Experiment No.	Date.	State of nutrition.	Duration of experiment.	R. Q.	Calories.	
					Indirect.	Direct.
	1920		hrs.			
47	May 13	Glucose.	2	1.01	44.56	42.17
50	" 20	"	2	1.01	44.71	43.66
Total..			4		89.27	85.83
44	May 10	Glucose + lactic acid.	2	1.07	44.33	42.69
46	" 12	" " " "	2	1.02	44.39	41.29
Total..			4		88.72	83.98
48	May 17	Glucose + acetic acid.	2	0.98	49.59	44.98
49	" 19	" " " "	2	0.97	49.76	45.42
Total..			4		99.35	90.40

Quite different results were obtained after giving acetic acid. Whereas with glucose alone the metabolism was 22.32 calories per hour, after adding acetic acid the heat production rose to 24.84 calories per hour, an increase of 2.52. But it has already been pointed out that after giving 3 gm. of acetic acid alone to this dog the metabolism was increased 3.13 calories.

The results may be thus expressed:

	Calories.	Per cent.
Glucose, 58 gm.....	+4.71	+27
Acetic acid, 3 gm.....	+3.13	+18
Sum of both.....	+7.84	+45
Glucose, 50 gm. + acetic acid, 3 gm.....	+7.23	+41

A true summation of effect is revealed similar to that found when glucose and fat are given together, and this supports the hypothesis that acetic acid is a normal intermediate in the metabolism of fatty acid. Since one theory of the production of fat from carbohydrate involves the production of acetaldehyde from methyl glyoxal by CO_2 cleavage and the subsequent polymerization of the aldehyde radicles into fatty acid, and since Lusk (7) has shown that the process of the conversion of fat into carbohydrate does not materially increase the heat production, one may still assume the *possibility* of a production of acetic acid from glucose in metabolism up to the limits of the power of the cell to oxidize acetaldehyde, following which maximum a synthetic production of fat ensues. At this point, however, ingested acetic acid might be oxidized and lift the metabolism to a higher level. It seems, however, more reasonable to believe that, if in the combustion of glucose by the cell acetic acid is produced as a dominant intermediate product, satisfying cell affinities for the oxidation of that substance, then the addition of a small quantity of acetic acid to the diet would not result in a quantitative reaction such as is noted above. Glucose ingestion does not change the CO_2 -combining power of the blood (5), therefore no acids are formed in its metabolism which diminish this power.

XI. ALCOHOL CHECKS.

The validity of the data presented rests upon the accuracy of the determinations. The following alcohol checks may reassure the reader. The calculated heat production and the theoretical oxygen consumption were estimated from the carbon dioxide production of the burning alcohol.

TABLE X.
Hourly Average of Alcohol Checks.

Experiment No.	Date.	R. Q.	Error on O ₂ .	Calories.		
				Indirect.	Direct.	Difference.
	1919		per cent			
66	Dec. 12	0.694	-3.9	22.37	22.40	+0.03
67	" 13	0.669	±0	17.47	17.90	+0.43
	1920					
68	Jan. 7	0.674	-1.1	23.32	23.56	+0.23
69	" 13	0.675	-1.1	24.53	24.51	-0.02
70	" 26	0.668	±0	23.70	24.02	+0.32
71	Feb. 3	0.662	±0	18.33	19.26	+1.33
72	" 13	0.632	+5.4	13.59	13.54	-0.05
74	" 17	0.659	+1.2	28.10	28.65	+0.55
77	Mar. 13	0.670	-0.5	27.35	26.60	-0.75
78	" 15	0.666	±0	24.49	24.86	+0.37
80	" 26	0.655	+1.7	22.59	22.55	-0.04
81	Apr. 19	0.684*	-2.5	24.21	23.40	-0.81
82	May 18	0.681	-2.1	26.94	25.66	-1.28
Average per hour..		0.669	-0.2	22.85	22.85	0

* Average of three hourly periods with R. Q. of 0.707, 0.667, 0.675.

XII. A GENERAL TABULATION.

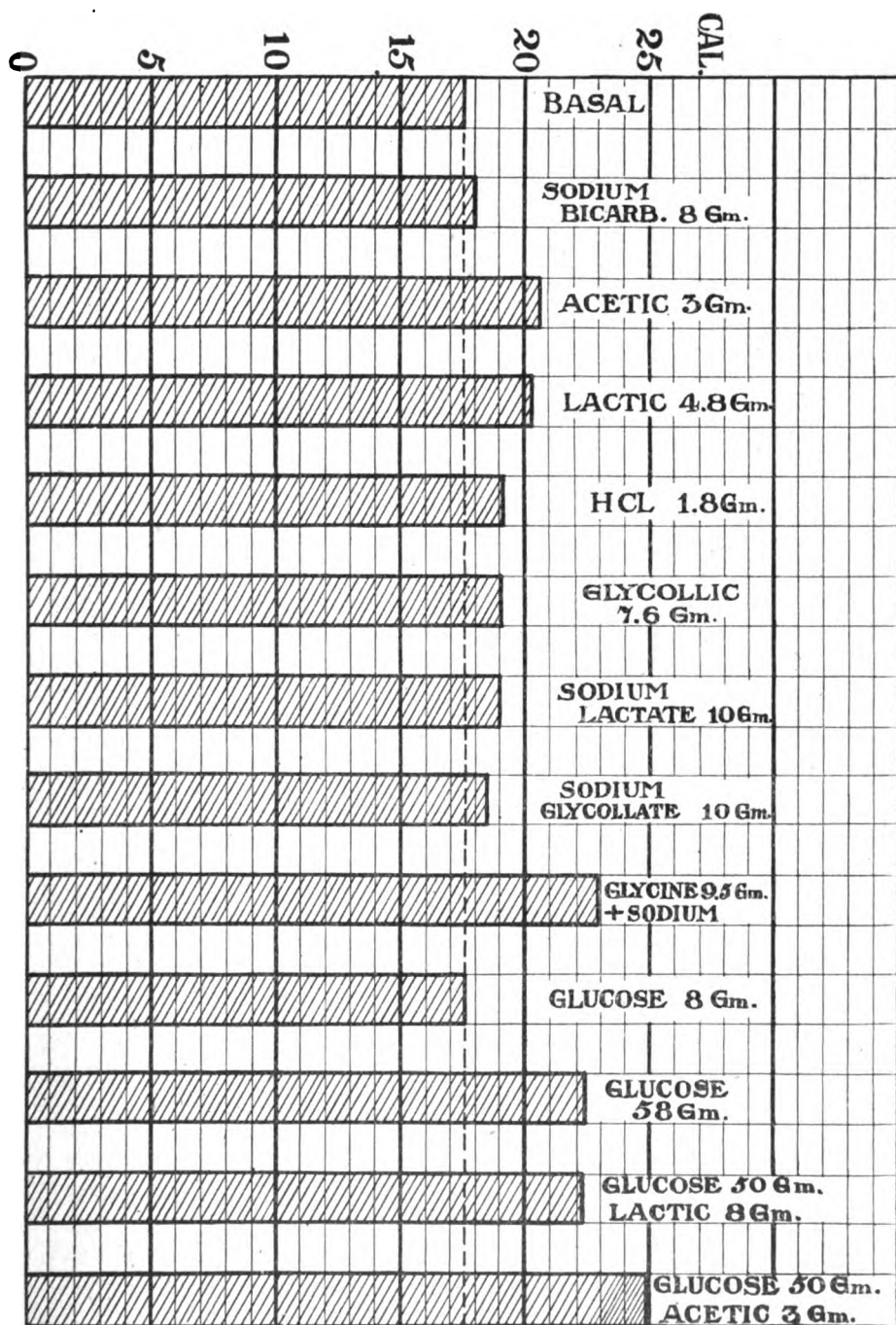
The results of this work are illustrated in the accompanying chart and are condensed into Table XI.

If one analyzes the experiments in which acids were given one finds no relation between the number of potential hydrogen ions administered and the height of the metabolism, nor is the power to reduce the carbon dioxide-combining power of the blood contributory.

This appears in the following table:

Substance given.	Relative number of potential H ions.	Increase in metabolism.	Decrease in CO ₂ -combining power of the plasma.
			per cent
Acetic acid, 3 gm.....	1.0	3.1	0
Lactic acid, 4.8 gm.....	1.2	2.7	14
Glycollic acid, 7.6 gm.....	2.0	1.5	28
HCl, 1.8 gm.....	1.0	1.6	11

CHART 1. The rise in calories above the basal metabolism which follows the ingestion of various metabolites.



It should be further noted that a quantity of glycine containing only 20 calories induced an increase in metabolism for 2 hours amounting to 5.3 calories per hour, while glucose containing 218 calories, or eleven times as many, raised the metabolism only by 4.7 calories. The glycocoll was neutralized with sodium before ingestion. While one may still speak of amino-acid stimulation in the sense that one speaks of the specific dynamic action of protein, one is still far removed from an actual elucidation of what transpires in the cells to induce the phenomenon.

TABLE XI.
A Summary of All the Experiments.

Nutritive condition.	Calories in diet.	R. Q.	Calories of metabolism per hour.		Num- ber of respira- tions per minute.	CO ₂ in each expira- tion. gm.
			Indi- rect.	Above basal.		
Basal metabolism.....	0	0.80	17.6		6	0.016
Liebig's extract.....	0	0.81	18.1	+0.5	8	0.012
NaHCO ₃ , 8 gm.....	0	0.83	18.05	+0.5	7	0.015
Acetic acid, 3 gm.....	10.5	0.78	20.7	+3.1	8.6	0.013
Lactic acid, 4.8 gm.....	17.6	0.84	20.3	+2.7	8.1	0.013
" " 8 " (Na salt).....	29.3	0.82	19.0	+1.4	7	0.015
Glycollic acid, 7.6 gm.....	16.8	0.94	19.1	+1.5	9	0.013
" " 7.6 " (Na salt).....	16.8	0.88	18.5	+0.9	7	0.015
HCl, 1.8 gm.....	0	0.84	19.2	+1.6	7.5	0.015
Glycine, 9.5 gm. + NaHCO ₃ , 10.7 gm.....	20.1	0.84	22.9	+5.3	10	0.013
Glucose, 58 gm.....	217.8	1.01	22.3	+4.7	10	0.014
" 50 " + lactic acid, 8 gm.....	217.0	1.04	22.2	+4.6	11	0.014
Glucose, 50 gm. + acetic acid, 3 gm.....	198.25	0.97	24.9	+7.2	12	0.013

The administration of these small quantities of materials to a dog is not easy, and the limitation of the method employed appears to me to have been reached in this research. Rubner (20), speaking in the Prussian Academy of Sciences in 1913, said, "Die Wanderung der Stoffe bis zur Zelle zu verfolgen, sie quantitativ zu messen und experimentell zu variieren, das gehört, bis heute wenigstens, zu den unlösbaren Aufgaben. Es ist auch kaum zu

erwarten, dass sich in Bälde die entgegenstehenden Schwierigkeiten überwinden lassen."

It is realized that the methods employed here are relatively crude and the results often merely suggestive.

XIII. SUMMARY.

1. The ingestion of 400 cc. of a broth containing 2.5 gm. of Liebig's extract of beef increased the heat production of a dog from a basal level of 16.1 calories by **0.5** calory per hour.

2. The addition of 8 gm. of sodium bicarbonate to the broth caused no further change in the metabolism.

3. The addition of 3 gm. of acetic acid to the broth caused an increase of **3.1** calories per hour. The material was evidently rapidly consumed.

4. Lactic acid, 4.8 gm. given as before, raised the basal metabolism by **2.7** calories. With 10 gm. of sodium lactate the heat production increased only **1.4** calories per hour, possibly because the alkali favored its transformation into glycogen.

5. Glycollic acid, 7.6 gm., with twice the number of potential H ions contained in it than were present in 3 gm. of acetic acid, increased the metabolism by **1.5** calories or less than half that effected by acetic acid. A like quantity given as glycollate of sodium increased the metabolism **0.88** calory.

6. Hydrochloric acid, 1.8 gm., caused the metabolism to increase **1.6** calories per hour.

7. Glycine, 9.55 gm., containing 20 calories and neutralized with sodium bicarbonate, caused the heat production to rise **5.3** calories per hour. Neutralization therefore did not avail to reduce the activity of the product.

8. Glucose, 58 gm., and glucose, 50 gm., plus lactic acid, 8 gm., manifest exactly the same increases above the basal metabolism, **4.7** and **4.6** calories respectively. Lactic acid therefore behaves like an intermediary metabolite of glucose and not like alanine which would have shown a summation effect.

9. Glucose, 50 gm., plus acetic acid, 3 gm., shows an increase of **7.23** calories per hour. This indicates a summation of the influences of the two factors involved; it is identical with the behavior of glucose and fat when given together; it supports the conception that acetic acid is an intermediary metabolism product

TABLE XII—General Summary

Date.	Experi- ment No.	Time.	CO ₂	O ₂	R. Q.	H ₂ O	Calories.			
							Protein.	Non- protein.	Indirect.	D
1920										
Jan. 12	4	11.52-12.52	7.02	6.86	0.74	8.05	3.50	18.96	22.46	21.4
		12.52- 1.52	6.52	6.09	0.78	7.21	3.50	16.59	20.09	21.4
									42.55	42.8
" 15	6	11.15-12.15	5.94	4.94	0.87	6.74	3.50	13.16	16.66	17.4
		12.15- 1.15	6.15	5.74	0.78	6.62	3.50	15.43	18.93	19.4
									35.59	36.8
" 16	7	11.11-12.11	6.05	5.46	0.81	6.09	3.50	14.62	18.12	17.4
		12.11- 1.11	5.93	5.60	0.77	6.08	3.50	14.91	18.41	18.4
									36.53	36.8
" 21	10	11.28-12.28	7.38	6.41	0.84	8.08	3.50	17.99	21.49	19.4
		12.28- 1.28	6.24	5.53	0.82	7.21	3.50	14.92	18.42	19.4
									39.91	38.8
" 22	11	11.30-12.30	7.52	6.35	0.86	7.14	3.50	17.92	21.42	19.4
		12.30- 1.30	6.65	5.92	0.82	7.20	3.50	16.22	19.72	20.4
									41.14	40.8
" 23	12	11.44-12.44	6.95	6.07	0.83	8.53	3.50	16.80	20.30	22.4
		12.44- 1.44	6.57	6.40	0.75	8.33	3.50	17.45	20.95	20.4
									41.25	42.8
" 27	13	1.40- 2.40	7.19	6.44	0.81	8.90	3.50	17.95	21.45	19.4
		2.40- 3.40	6.00	5.87	0.74	8.09	3.50	15.68	19.18	19.4
									40.63	38.8
" 28	14	11.23-12.23	6.51	5.87	0.81	8.20	3.50	16.00	19.50	20.4
		12.23- 1.23	6.49	5.85	0.81	7.98	3.50	15.93	19.43	22.4
									38.93	43.8
Feb. 5	19	11.47-12.47	5.91	4.92	0.87	8.49	3.50	13.09	16.59	16.4
		12.47- 1.47	5.52	4.99	0.80	7.76	3.50	13.03	16.53	16.4
									33.12	33.4
" 6	20	11.30-12.30	7.37	6.09	0.88	9.49	3.50	17.13	20.63	14.4
		12.30- 1.30	7.18	5.33	0.98	8.59	3.50	14.88	18.38	17.0
									39.01	31.8

XIX.

by temperature.		Morning weight.	Behavior of dog.	Food.
End.	Difference.			
		kg.		
38.06	-0.20	10.60	Quiet. Single movements.	Acetic acid, 3 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.40 a.m.
37.76	-0.19	10.57	Quiet. Slight movements.	Basal metabolism.
37.90	-0.30	10.57	Moving 1 minute. Quiet.	Meat extract, 2.5 gm.; water, 350 cc. at 10.30 a.m.
37.96	+0.05	10.57	Slight movement. Occasional movement.	Lactic acid, 4.8 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.17 a.m.
38.21	+0.08	10.55	Slight movement. Single movements.	Lactic acid, 4.8 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.40 a.m.
38.14	-0.11	10.52	Quiet. Moving 3 minutes.	Acetic acid, 3 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.21 a.m.
38.12	-0.11	10.32	3 slight movements. Quiet.	Acetic acid, 3 gm.; meat extract, 2.5 gm.; water, 400 cc. at 12.35 p.m.
38.45	+0.30	10.35	Slight movement. Manyslightmovements.	Water, 400 cc.; meat extract 2.5 gm. at 10.34 a.m.
38.10	-0.11	10.27	Quiet. "	Basal metabolism.
37.73	-0.34	10.30	Quiet. "	Glycollic acid, 7.6 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.35 p.m.

TABLE

Date.	Experi- ment No.	Time.	CO ₂	O ₂	R. Q.	H ₂ O	Calories.			
							Protein.	Non- protein.	Indirect.	D.
1940			gm.	gm.		gm.				
Feb. 9	21	11.20-12.20	6.72	5.93	0.82	8.35	3.50	16.29	19.79	19.7
" 18	22	11.16-12.16	7.22	5.55	0.95	9.93	3.50	15.59	19.09	18.7
		12.16- 1.16	7.09	5.29	0.97	7.86	3.50	14.74	18.24	17.7
									37.33	36.4
" 19	23	12.36- 1.36	5.84	5.12	0.83	7.56	3.50	13.58	17.08	13.1
		1.36- 2.36	5.69	5.19	0.80	7.48	3.50	13.67	17.17	13.1
									34.25	37.1
Mar. 16	24	11.28-12.28	6.26	5.30	0.86	10.23	3.21	14.65	17.86	15.1
		12.28- 1.28	5.42	5.37	0.73	8.97	3.21	14.30	17.51	15.1
									35.37	31.3
" 19	25	11.40-12.40	5.88	5.15	0.83	9.34	3.50	13.68	17.18	17.2
		12.40- 1.40	5.64	5.34	0.77	8.48	3.50	14.04	17.54	16.1
									34.72	34.1
" 20	26	10.57-11.57	6.99	5.46	0.93	9.58	3.50	15.20	18.70	16.4
		11.57-12.57	7.08	5.76	0.89	8.83	3.50	16.07	19.57	17.1
									38.27	34.1
" 27	28	11.00-12.00	6.63	5.63	0.86	10.85	3.50	15.43	18.93	17.1
		12.00- 1.00	6.64	5.80	0.83	9.99	3.50	15.89	19.39	17.1
									38.32	34.1
" 30	29	2.28- 3.28	5.61	5.19	0.78	9.15	3.50	12.10	17.04	17.3
		3.28- 4.28	6.07	6.02	0.73	8.72	3.50	14.62	19.55	18.3
									36.59	36.1
Apr. 6	32	1.06- 2.06	5.82	5.41	0.78	8.22	3.50	14.33	17.83	17.0
		2.06- 3.06	5.65	5.75	0.71	8.27	3.50	15.19	18.69	18.7
									36.52	35.7
" 8	33	12.05- 1.05	6.57	5.75	0.83	9.02	3.50	15.72	19.22	17.9
		1.05- 2.05	6.26	5.70	0.80	8.91	3.50	15.39	18.89	18.3
									38.11	36.2

Continued.

Body temperature.		Morning weight.	Behavior of dog.	Food.
End.	Difference.			
		kg.		
38.48	-0.12	10.27	Moving 3 minutes.	Meat extract, 2.5 gm.; water, 400 cc. at 10.40 a.m.
37.44	-0.17	10.05	1 minute slight action. Quiet.	Glycollic acid, 7.6 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.88 a.m.
37.67	+0.10	10.05	Slight movement. Restless.	Meat extract, 2.5 gm.; water, 400 cc. at 10.50 a.m.
38.05	-0.32	10.02	Quiet. "	Basal metabolism.
37.90	-0.07	10.00	Slight movement. " "	Meat extract, 2.5 gm.; water, 400 cc. at 10.50 a.m. Some vomited and water given in place of vomitus.
37.78	-0.19	10.01	3 minutes slight action. 2 " " "	Glycollic acid, 7.6 gm.; meat extract, 2.5 gm.; water, 400 at 10 a.m.
37.99	-0.20	10.05	Quiet. Slight movement.	HCl, 1.8 gm.; meat extract, 2.5 gm.; water, 300 cc. at 10.11 a.m.
		9.90	Quiet. "	Basal metabolism.
37.76	-0.08	9.85	Quiet. "	Basal metabolism.
38.05	-0.17	9.80	Quiet. "	Lactic acid, 8 gm.; NaHCO ₃ , 8 gm.; meat extract, 2.5 gm.; water, 400 cc. at 11.17 a.m.

Date.	Experi- ment No.	Time.	CO ₂	O ₂	R. Q.	H ₂ O	Calories.			
							Protein.	Non- protein.	Indirect	D.
1920			gm.	gm.		gm.				
Apr. 9	34	11.28-12.28	5.99	5.35	0.81	8.91	3.50	14.28	17.78	16.1
		12.28- 1.28	5.49	4.85	0.82	8.13	3.50	12.63	16.13	16.1
									33.91	32.2
" 12	35	12.25- 1.25	5.58	5.15	0.79	8.45	3.50	13.49	16.99	16.1
		1.25- 2.25	5.82	5.38	0.79	8.06	3.50	14.26	17.76	17.1
									34.75	34.1
" 13	36	12.40- 1.40	6.63	5.99	0.81	11.83	3.50	16.39	19.89	18.1
		1.40- 2.40	6.11	5.44	0.82	10.69	3.50	14.60	18.10	17.1
									37.99	35.1
" 20	37	11.38-12.38	7.04	5.73	0.89	10.80	3.50	15.96	19.46	17.1
		12.38- 1.38	6.31	5.43	0.85	9.80	3.50	14.70	18.20	16.1
		1.38- 2.38	6.46	5.25	0.89	9.43	3.50	14.31	17.81	17.1
									55.47	50.1
" 21	38	1.34- 2.34	5.65	5.10	0.81	12.53	3.50	13.40	16.90	16.1
" 22	39	11.16-12.16	8.35	7.18	0.85	6.96(?)*	7.91†	15.82	23.78	23.1
		12.16- 1.16	7.77	6.70	0.84	6.96	7.91†	14.25	22.16	21.1
		1.16- 2.16	6.33	5.85	0.79	6.41	6.51†	12.64	19.15	19.1
									65.09	61.1
May 1	42	10.44-11.44	6.56	5.32	0.90	11.26	3.50	14.56	18.06	19.1
		11.44-12.44	6.22	5.81	0.78	10.49	3.50	15.66	19.16	18.1
									37.22	37.1
" 4	43	1.02- 2.02	5.77	5.09	0.82	14.44	3.50	13.45	16.95	17.1
" 10	44	11.32-12.32	9.14	5.96	1.12	12.71	3.50	17.61	21.11	21.1
		12.32- 1.32	9.36	6.64	1.03	12.33	3.50	19.72	23.22	20.1
		1.32- 2.32	9.12	6.69	0.99	11.81	3.50	19.77	23.27	20.1
									67.60	63.1
" 12	46	11.24-12.24	8.87	6.68	0.97	14.13	3.50	19.64	23.14	21.1
		12.24- 1.24	8.90	6.04	1.07	12.75	3.50	17.75	21.25	19.1
		1.24- 2.24	9.27	6.60	1.02	11.73	3.50	19.57	23.07	22.1
									67.46	63.1

* Water estimated.

† Including amino-acid.

inued.

y temperature.		Morning weight.	Behavior of dog.	Food.
End.	Difference.			
		kg.		
37.73	-0.26	9.90	Quiet. "	Meat extract, 2.5 gm.; water, 400 cc. at 10.30 a.m.
38.01	-0.34	9.80	Quiet. "	Basal metabolism.
38.07	-0.12	9.80	Quiet. "	Lactic acid, 8 gm.; NaHCO_3 , 7.6 gm.; meat extract, 2.5 gm.; water, 400 cc. at noon.
37.38	-0.17	9.67	Quiet. " "	Sodium glycocholate, 10 gm.; meat extract, 2.5 gm.; water, 400 cc. at 11 a.m.
37.84	-0.08	9.65	Quiet.	Basal metabolism.
38.42	+0.42	9.65	Quiet. " "	Glycine, 9.55 gm.; NaHCO_3 , 10.7 gm.; meat extract, 2.5 gm.; water, 300 cc. at 10.33 a.m.
38.00	-0.18	9.60	Quiet. 3 minutes moving.	NaHCO_3 , 8 gm.; meat extract, 2.5 gm.; water, 300 cc. at 10.10 a.m.
37.85	-0.28	9.60	Quiet.	NaHCO_3 , 8 gm.; meat extract, 2.5 gm.; water, 300 cc. at 11.08 a.m.
38.48	± 0	9.55	Quiet. " "	Glucose, 50 gm.; lactic acid, 8 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.35 a.m.
38.14	+0.10	9.65	3 minutes movement. 3 " " Slight "	Glucose, 50 gm.; lactic acid, 8 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.30 a.m.

Date.	Experi- ment No.	Time.	CO ₂	O ₂	R. Q.	H ₂ O	Calories.			
							Protein.	Non- protein.	Indirect.	D.
1980			gm.	gm.		gm.				
May 13	47	11.38-12.38	8.80	6.36	1.01	13.81	3.50	18.66	22.16	21
		12.38- 1.38	8.96	6.42	1.02	12.87	3.50	18.90	22.40	21
		1.38- 2.38	8.18	6.21	0.96	11.73	3.50	17.95	21.45	21
									66.01	63
" 17	48	11.05-12.05	9.46	6.93	0.99	12.04	3.50	20.63	24.13	21
		12.05- 1.05	9.72	7.35	0.96	12.33	3.50	21.96	25.46	21
		1.05- 2.05	7.86	6.42	0.89	11.84	3.50	18.32	21.82	20
									71.41	68
" 19	49	11.24-12.24	9.57	7.43	0.94	14.18	3.50	22.08	25.58	22
		12.24- 1.24	9.52	6.94	1.00	12.99	3.50	20.68	24.18	22
		1.24- 2.24	7.56	5.82	0.94	12.01	3.50	16.52	20.02	19
									69.78	65
" 20	50	11.28-12.28	9.04	6.55	1.00	15.27	3.50	19.32	22.82	22
		12.28- 1.28	8.78	6.27	1.02	13.51	3.50	18.39	21.89	21
		1.28- 2.28	8.26	5.86	1.03	13.12	3.50	16.96	20.46	19
									65.17	62

cluded.

Body temperature.		Morning weight.	Behavior of dog.	Food.
End.	Difference.			
38.18	+0.05	9.70	Quiet. " 1½ minutes moving.	Glucose, 58 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.40 a.m.
38.21	-0.06	9.70	Quiet. " "	Glucose, 50 gm.; acetic acid, 3 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.05 a.m.
38.33	+0.28	9.70	Restless. Quiet. "	Acetic acid, 3 gm.; glucose, 50 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.25 a.m.
38.14	+0.17	9.72	3 minutes movement. Quiet. 3 minutes movement.	Glucose, 58 gm.; meat extract, 2.5 gm.; water, 400 cc. at 10.40 a.m.

of fatty acid by β -oxidation; it renders questionable the idea that acetic acid is an intermediary product of glucose metabolism.

I wish to express my obligation to Miss Sophia A. Taistra who made the urinary analyses and assisted in the entire work.

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ANIMAL CALORIMETRY.

NINETEENTH PAPER.

THE INFLUENCE OF ACIDS UPON THE CARBON DIOXIDE-COMBINING POWER OF THE BLOOD PLASMA.

By SOPHIA A. TAISTRA.

(From the Physiological Laboratory of Cornell University Medical College,
New York City.)

(Received for publication, October 13, 1921.)

The demonstration by Lusk (1) that the ingestion of glycine and alanine caused great increases in the heat production has led to the question, considered in the last paper, whether acid radicles are the cause of those increases in metabolism defined under the head of the specific dynamic action of foodstuffs. In former papers of this series the influence of the concentration of glucose, amino-acids, and of fat in the blood, as bearing upon the intensity of the metabolism of those substances in the cells, has been discussed. This paper deals with the reduction in the quantity of sodium bicarbonate in the blood after administering acid substances to Dog XIX in quantities which are comparable with the amounts which were given to it in the calorimeter experiments described in the last paper. It is known that the reduction in alkali reserve of the blood plasma does not change the actual hydrogen ion concentration of the medium. The method used was to determine the change in the carbon dioxide-combining power of the plasma with the apparatus of Van Slyke.

Van Slyke, Stillman, and Cullen (2) have found in man that, after taking a "mixed diet" at breakfast, the CO_2 -combining power of the blood was usually increased, which does not indicate a production of acid metabolites as a cause of the specific dynamic action of the ingested food.

The different substances were always given in a broth containing Liebig's extract of beef. The results may thus be tabulated:

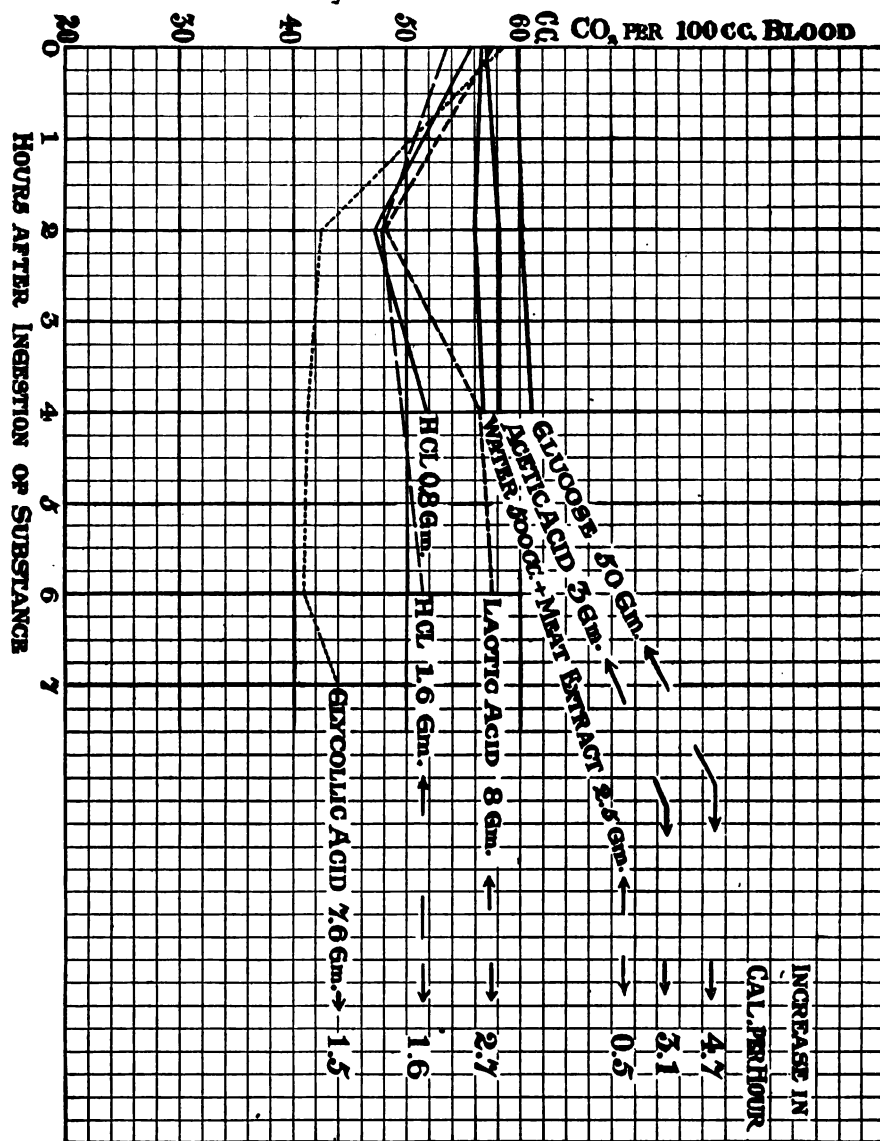
TABLE I.
Influence of Various Metabolites upon the CO₂-Combining Power of the Blood Plasma of Dog XIX.

Date.	Experi- ment No.	State of nutrition.	Volume of broth given.	CO ₂ - combining power of plasma.						Rise or fall at 2nd hr.	Probable rise above basal of 17.6 calo- ries per hr.
				Start.	Hrs. after the start.						
					2	4	6	7			
			cc.						per cent	calories	
1919											
Oct. 22	1	Liebig's extract, 2.5 gm.	500	56.7	56.0	56.7				-1.2	+0.5
" 24	2	Glucose, 50 gm.	500	58.5	57.0	59.5				-2.5	+4.7
Nov. 1	3	" 50 "	150	59.9	60.1	61.0				+1.7	+4.7
Dec. 22	4	Acetic acid, 2.5 gm.	500	58.5	58.5						+3.1
1920											
Jan. 5	5	" " 3 gm.	400	57.1	58.1	58.1				+1.7	+3.1
Feb. 20	6	Glycollic acid, 7.6 gm.	400	58.4	42.4	41.4	41.0	44.0		-27.6	+1.5
1919											
Oct. 20.	7	Lactic acid, 8 gm.	500	58.7	49.0	53.8	53.8			-14.0	+2.7†
1920											
Feb. 20	8	" " 8 "	500	59.5	51.0	56.7				-14.2	
May 22	9	" " 8 "	400	57.6	48.1	56.5	57.5			-16.4	
Mar. 22	10	HCl, 0.8 gm.	400	55.7	47.1	51.9				-15.6	
1921											
May 26	11*	HCl, 1.8 gm.	500	53.5	47.8	49.7	51.6			-10.8	+1.6

* This experiment was performed by Mr. Chanutin.

† Consult also Atkinson and Lusk (3).

CHART 1. Showing the curves of the carbonic acid-combining power of the blood plasma after giving various metabolites to a dog.



It is evident from this that glucose, 50 gm., and acetic acid, 3 gm., which cause the greatest increases in metabolism, have no effect whatever upon the carbon dioxide-combining power of the blood, whereas glycollic acid, lactic acid, and hydrochloric acid, which have comparatively little influence upon the heat production, produce a profound depression of the CO_2 -combining power. The specific dynamic influence of the foodstuffs is therefore not attributable to the introduction of acid metabolites in the blood stream. Chart 1 illustrates these relations.

The absence of any effect upon the CO_2 -combining power after giving acetic acid indicates its rapid utilization. The fact that

TABLE II.

Influence of Various Metabolites upon the Acidity of the Urine of Dog XIX.

Experiment No.	State of nutrition.	Volume of broth given.	Urine.		
			Period.	Volume.	0.1 N alkali in cc. per hour to neutralise urine.
		cc.	hrs.	cc.	cc.
1	Liebig's extract, 2.5 gm.	500	5	405	6.3
2	Glucose, 50 gm.	400	4	355	2.6
3	" 50 "	150	4	155	1.8
4	Acetic acid, 2.5 gm.	500	2	390	6.0
5	" " 3 "	400	2	270	6.3
6	Glycollic acid, 7.6 gm.	400	2	245	25.6
7	Lactic acid, 8 gm.	500	6	526	12.3
	" " 8 "	500	4	340	12.3
10	HCl, 0.8 gm.	200	4	145	4.4
	HCl, 1.6 "	300	4	225	11.8

glucose, given in the excess here provided, causes no change in the CO_2 -combining power, indicates that no lactic acid can be produced from it in such a manner as to influence by neutralization the alkali reserve of the blood. If lactic acid is formed intracellularly or upon the surface of the cell during the metabolism of glucose, thereby producing a stimulation of metabolism, its effect must be strictly local as it cannot modify the alkaline reserve of the blood. The above experiments demonstrate that lactic acid, if it once enters the blood, may cause a significant fall in the alkali reserve.

In several of the above experiments the urine was titrated to the neutral point, using 0.1 N NaOH against phenolphthalein as indicator.

The results appear in Table II.

The figures here reported merely emphasize the fact that after giving glucose and acetic acid the blood is under no necessity of compensating for a gain in acid radicles by eliminating such through the kidney, whereas in the case of glycollic and lactic acids such a stress is indicated.

CONCLUSION.

The specific dynamic action of the foodstuffs is not dependent upon the level of the alkaline reserve of the blood plasma as measured by its CO₂-combining power.

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ANIMAL CALORIMETRY.

TWENTIETH PAPER.

THE INFLUENCE OF THE INGESTION OF MEAT AND OF GLYCINE AND ALANINE UPON THE CARBON DIOXIDE-COMBINING POWER OF BLOOD PLASMA.

By ALFRED CHANUTIN.

(From the Physiological Laboratory of Cornell University Medical College,
New York City.)

(Received for publication, October 13, 1921.)

The problem is but an extension of that presented in the last two papers and may be stated in the words: Do the amino-acids formed after the ingestion of meat by a dog so reduce the alkali reserve of the blood that this becomes a contributing cause of the great increase in heat production known as the specific dynamic action of meat? Hasselbalch (1) observed a lower CO_2 tension of the alveolar air after administering a meat diet to a man than

TABLE I.

Influence of Meat, Glycine, and Alanine Ingestion upon the CO_2 -Combining Power of the Blood Plasma of the Dog.

Date.	Experiment No.	State of nutrition.	CO ₂ -combining power of 100 cc. of plasma.						
			Start.	Hrs. after the start.					
				1	2	3	4	5	6
1920									
Sept. 27	1	Beef, 940 gm.	59.8		68.7		63.0		63.4
Oct. 5	2	" 810 "	64.8	71.3	61.5		63.0	64.6	65.6
" 14	3	" 1,000 "	61.9	63.8	64.8	69.4	68.4	67.5	61.0
1921									
May 21	4	" 1,000 "	65.0	65.5	69.4		70.3		69.4
" 11	5	Glycine, 15 gm.	58.4	63.3	64.2		62.2		
" 13	6	" 15 "	62.9	69.6	64.7		60.9		
Apr. 13	7	Alanine, 15 gm.	65.7	69.5	67.6				
May 9	8	" 15 "	65.9	67.8	67.8		66.8	65.0	

after giving an alkaline vegetarian diet, which might be interpreted as signifying that the latter caused a greater increase in the alkaline reserve than was brought about by the meat diet.

The amino-acids were administered as heretofore in a warm broth containing 2.5 gm. of Liebig's extract and 500 cc. of water.

It is apparent from Table I that there is always an increase in the CO_2 -combining power of the blood following the ingestion of meat, of glycine, or of alanine. The broth itself was without influence.

It is possible that the interpretation of Erdt (2) is correct, that the rise in the CO_2 tension in the alveoli which follows the taking of a meal is due to the secretion of hydrochloric acid by the gastric juice.

CONCLUSION.

It is apparent that the ingestion of meat or of amino-acid derivatives of meat may materially increase the alkali reserve of the organism of a dog, as measured by the CO_2 -combining power of the blood plasma. Since the administration of bicarbonate of sodium has no influence upon the heat production of a dog (Paper 18), it is evident that the great increase in the heat production which takes place during the hours immediately after the ingestion of meat is not determined by any change in the alkaline reserve of the blood, nor can such change be interpreted as being even a participating element in the causation of the phenomenon.

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ANIMAL CALORIMETRY

TWENTY-FIRST PAPER

THE INFLUENCE OF MORPHINE UPON HEAT PRODUCTION IN THE DOG

ALFRED CHANUTIN AND GRAHAM LUSK

WITH THE TECHNICAL ASSISTANCE OF MR. JAMES EVENDEN

*From the Physiological Laboratory of Cornell University Medical College,
New York City*

Received for publication October 15, 1921

I. INTRODUCTION

Ordinary observation of the action of morphine on the organism would naturally lead to the conclusion that the metabolism is lowered, since there is a lessened rate of respiration, slower pulse and a lower body temperature. The evidence at hand, however, is inconclusive.

Von Boeck (1) in 1871 determined the influence of morphine on the protein metabolism of a dog in nitrogen equilibrium and concluded that it was reduced by 6 per cent. Underhill, Goldschmidt and Blatherwick (2), however, found a definite increase in the urinary nitrogen output after injecting morphine in a starving dog.

Bloor (3) found that the fat content of the blood was unchanged during morphine narcosis but that a lipemia resulted two days later.

Luzzatto (4) and Araki (5) first demonstrated the presence of a reducing sugar in the urine of rabbits and dogs after large doses of morphine. A study of the blood-sugar content was made by Ross (6) after injections of morphine (10 mgm. per kilogram body weight). The analyses were continued until one and a half hours after the injections, but no results are given to

indicate when the normal blood-sugar level was restored. A maximum increase of 77 per cent in the blood-sugar content was obtained one and one-half hours after the injection of morphine.

The output of carbon dioxide and the consumption of oxygen in cats and dogs after administering morphine were studied by von Boeck and Bauer (7) as early as 1874. They found that there was an increased respiratory exchange in the excited cat but that in the narcotized dog the carbon dioxide output was reduced 27 per cent and the oxygen consumption, 34 per cent. Voit (8) concludes from these results that morphine affects metabolism only indirectly because of decreased muscular activity; that in narcosis, as in sleep, there is a reduction in the production of heat. Normal control animals were not at that time restricted in their movements during the measurement of their metabolism.

The oxygen consumption of two human beings in normal and morphine sleep was studied by Loewy (9) and in both cases there was found to be a slight decrease of oxygen utilization after morphine administration. He concludes that morphine does not materially affect the respiratory exchange. Higgins and Means (10) obtained diabetic quotients on themselves after therapeutic doses of morphine. The experiment was continued for two hours after administration of the drug. The respiratory exchange showed no alteration in the consumption of oxygen, but there was a marked drop in carbon dioxide elimination.

The alkali reserve of the blood plasma is either unaltered or slightly depressed during sleep (Collip (11)). Hjort and Taylor (12) and Gauss (13) found an increased alkali reserve in narcotized dogs after morphine.

The purpose of this investigation is to study the effects of subcutaneous injection of morphine upon the basal metabolism of dogs.

II. METHODS

Two trained calorimeter dogs, which had received the "standard diet" at 5 p.m. the day previously, were used in these experiments. Doses varying from 12 mgm. to 20 mgm. of mor-

phine (in 2 per cent solution) per kilogram body weight were injected subcutaneously, and the dog was placed in the calorimeter immediately after vomiting and defecation had ceased. The urine for the period was collected by catheterization.

The basal metabolism was determined at frequent intervals about eighteen hours after administration of a standard diet when the dog was resting quietly in the calorimeter at a temperature of 26°C. It is important to note that the trained dog remains quiet or asleep throughout the experiment.

III. BASAL METABOLISM

The determinations of the basal metabolisms of the two dogs may be summarized as shown in table 1.

TABLE 1
Basal metabolisms of dogs XVIII and XIX

NUMBER OF EXPERIMENT	DATE	HOURS OF EXPERIMENT	R. Q.	CALORIES	
				Indirect	Direct
Dog XVIII					
76A	1921 February 11	2	0.82	32.36	30.45
77	February 12	2	0.75	32.24	30.83
78	February 17	2	0.82	34.31	37.47
80A	February 25	1	0.83	17.12	17.04
Sum.....		7		116.03	115.79
Average per hour.....			0.81	16.58	16.54
Dog XIX					
55A	February 4	2	0.79	34.58	32.71
57	February 15	1	0.82	17.47	18.09
59	February 23	2	0.85	35.38	36.45
Sum.....		5		87.43	87.25
Average per hour.....			0.82	17.49	17.45

These results may be compared with former determinations upon these dogs as follows:

	DOG XVIII	DOG XIX
Date.....	Exp. 57, May 9, 1919	Jan. to Apr., 1920
Weight in kilograms.....	10.8	10.6 to 9.6
Calories of metabolism.....	16.6	17.61
<i>Present series (1921):</i>		
Weight in kilograms.....	11.05 to 10.65	9.65 to 9.15
Calories of metabolism.....	16.56	17.49

Two years of continuous confinement in a metabolism cage did not change the basal metabolism of dog XVIII.

IV. ADMINISTRATION OF MORPHINE

The two dogs behaved differently after administering morphine. Dog XVIII was usually absolutely quiet throughout the period

TABLE 2
Influence of morphine upon the basal metabolisms of dogs XVIII and XIX

NUMBER OF EXPERI- MENT	DATE	HOURS OF EXPERI- MENT	MORPHINE PER KILOGRAM	R. Q.	CALORIES	
					Indirect	Direct
Dog XVIII						
	1921		mgm.			
76B	February 11	3	15	0.79	47.29	40.73
79	February 18	4	15	0.85	62.17	61.91
80B	February 25	3	15	0.84	44.81	?
81	March 1	3	15	0.78	47.91	47.86
Sum.....		13			202.18	
Average per hour.....				0.82	15.55	
Dog XIX						
55B	February 4	2	12	0.90	35.23	33.55
58	February 16	3	20	0.87	61.18	54.83
60	February 24	2	15*	0.84	43.00	42.67
61	February 28	4	15†	0.82	74.90	74.50
Sum.....		11			214.31	205.55
Average per hour.....				0.86	19.48	18.69

*With ether and chloroform.

†With ether.

of experimentation, whereas dog XIX showed increased irritability, with heightened reflexes. An attempt was made to more heavily anesthetize this animal by giving ether or ether and chloroform but without entire success.

The results obtained may be summarized as shown in table 2.

These results show that in dog XVIII the administration of morphine reduced the basal metabolism from 16.56 to 15.54 calories per hour, an average fall of 6.2 per cent; whereas in dog XIX the metabolism was increased from 17.49 to 19.48 calories, a rise of 10 per cent.

If one considers the heat production in the first experimental hours in the morphine experiments upon dog XVIII one finds an average of 14.7 calories per hour. This represents an average reduction of 11 per cent in the basal metabolism of this dog. The metabolism usually returned to the normal basal level in the third and fourth hours, even though the body temperature was lowest during these hours, as may be seen below:

DOG XVIII	EXPERIMENT 76B	EXPERIMENT 79	EXPERIMENT 80B	EXPERIMENT 81	AVERAGE REDUCTION BELOW THE BASAL VALUE
					<i>per cent</i>
2nd hour.....	14.44	14.73	13.71	15.80	11
3rd hour.....	16.42*	15.22	15.78	15.08	6
4th hour.....	16.42*	15.38	15.32	17.03	4
5th hour.....		16.84			

* Not separately determined.

In the excitable dog XIX no analogous diminution of metabolism was noted. The highest metabolism, at the rate of 21.5 calories per hour, was observed when morphine, chloroform and ether were administered together. This is an increase of 4 calories, or 23 per cent, above the basal metabolism. As the activity of the dog was less than when morphine and ether were given together one may surmise a calorigenetic action on the part of chloroform. The usual fall in body temperature did not occur in this experiment, so this factor as an element in reducing metabolism was not in evidence.

The respiratory quotients in dog XIX rose somewhat after the administration of morphine. This may be due to the well-known preference of active muscle for carbohydrate. In dog XVIII, at least, the great increase in blood-sugar after giving morphine, which was reported by Ross, apparently had little effect qualitatively or quantitatively upon the metabolism of the animal.

V. THE MANNER OF HEAT LOSS

During the determination of the basal metabolism it is often noted that the rectal temperature of the quiet dog falls a few tenths of a degree. Such a fall denotes a loss of the body's heat to the external air by radiation and conduction. After the administration of morphine the body temperature of the dogs fell between 0.95 and 2.05°C. during the experimental periods, except in the one instance already mentioned when ether and chloroform were also administered.

In experiment 77, in which a determination of the basal metabolism was made on dog XVIII, 23.82 (72 per cent) calories were eliminated by radiation and conduction and 9.21 (28 per cent) by vaporization of water from the lungs, a total of 33.03 calories in two hours. The calculated metabolism of the period was 32.24 calories. The dog's body lost in temperature 0.24°C., as measured by the rectal thermometer, a loss which is the equivalent of 2.2 calories eliminated from his body. $[11 \text{ (kgm. body weight)} \times 0.83 \text{ (specific heat of the body)} \times 0.24 \text{ (fall in body temperature)} = 2.2 \text{ calories eliminated.}]$ Deducting this from the 33.03 calories "eliminated," one obtains 30.83 calories as calories "produced," which are the calories directly measured. In long experiments, in which the changes in the body temperature play a negligible part in the results obtained, the calculated calories (indirect calorimetry) correspond with the calories produced (direct calorimetry). The body temperature is best measured by the rectal thermometer, but there are evidently indeterminable factors here which render exactness impossible. If one assumes that the above calculation by indirect calorimetry gives the more correct value of the actual amount of heat pro-

duced, then one may state that of the 32.24 calories which were produced 33.03 were eliminated; also, that when 100 were produced 74 were lost by radiation and conduction, 29 by the evaporation of water, a total of 103. Three per cent more calories (0.79 calorie) were therefore eliminated than were produced.

Understanding these principles, one may analyze from the accompanying table 3 the profound losses of heat from the dog's body after giving morphine. For example, in experiment 81 on dog XVIII the rectal thermometer indicates a cooling of the dog's tissues which corresponds to a loss of 18.12 calories during three hours. Indirect calorimetry indicates a production of heat amounting to 47.91 calories, while the heat loss measured by the calorimeter was 65.98 calories, or 18.07 calories more than were produced, as estimated by indirect calorimetry. The results check perfectly. Thirty-six per cent more calories were lost from the body than were produced. More heat was lost by radiation and conduction alone (106 per cent) than was produced during the interval. All this indicates a distribution of heat to the area of the skin by relaxed blood vessels. The demonstrated increased loss of heat by radiation and conduction from the skin recalls the dilation of the superficial blood vessels in man after the administration of Dovers powder, which contains morphine and ipecac. Though the heat eliminated per hour is 22 calories, or 32 per cent above the basal level, the heat production is 16 calories, or only 4 per cent below that level. The reduction of metabolism by approximately half a calorie an hour cannot possibly be the cause of a loss of 6 calories per hour with the consequent fall in body temperature. The relative methods of heat loss are not materially changed from the normal, for 22 per cent of the calories were eliminated by vaporization of water, 78 per cent by radiation and conduction. The average of the four normal periods shows a heat loss of 26 per cent by the vaporization of water.

In experiment 80B the average heat loss from the body is 4.6 calories per hour above the heat production as calculated by the indirect method, whereas this heat production is only 1.6 calories below the basal level.

TABLE 3
Influences of morphine upon the manner of heat loss; values in calories per hour

	DOG XVIII				DOG XIX			
	Experi- ment 76B	Experi- ment 79	Experi- ment 80B	Experi- ment 81	Experi- ment 55B	Experi- ment 58	Experi- ment 60 plus chlo- roform and ether	Experi- ment 61 plus ether
	<i>calories</i>	<i>calories</i>	<i>calories</i>	<i>calories</i>	<i>calories</i>	<i>calories</i>	<i>calories</i>	<i>calories</i>
Basal metabolism.....	16.56	16.56	16.56	16.56	17.49	17.49	17.49	17.49
Indirect calorimetry after morphine.....	16.76	15.64	14.94	15.97	17.61	20.39	21.50	20.51
Change from basal.....	-0.80	-1.02	-1.62	-0.59	+0.12	+2.90	+4.01	+3.02
Calories eliminated*.....	18.65	18.42	19.56	22.00	20.46	22.43	21.50	20.51
Indirect calorimetry.....	16.76	15.64	14.94	15.97	17.61	20.39	21.50	18.72
Loss of calories from body.....	-2.89	-2.88	-4.62	-6.03	-2.85	-2.04	±0	-1.79
Same (calculated from rectal temperature).....	-5.08	-2.85		-6.04	-3.46	-4.15	-0.32	-3.84
Per cent of calories eliminated in water vapor.....	25	20	18	23	21	21	21	26

* By radiation and conduction and by vaporization of water. The latter factor in dog XVIII was 26, in dog XIX 23 per cent of the total in the average of 4 and 3 determinations of the basal metabolism.

Perhaps even more striking are the results upon the irritable dog XIX. Calculated by the same method there is an hourly excess of heat loss of 2 calories from the animal's body in experiment 58, despite an increase in the heat production of 2.90 calories above the basal level. The heat loss by vaporization of water was 21 per cent, in contrast with 23 per cent as the average of three determinations of the basal metabolism.

The results of all the experiments in which morphine was given may be briefly condensed into table 3.

Consideration of this table shows that, except in the case in which chloroform was also administered, there was in every instance following the administration of morphine a loss of heat from the body which was not compensated for by a corresponding increase in metabolism, as is normally the case. This loss of heat occurred in a quiet resting dog (dog XVIII) despite the fact that the decrease in heat production was relatively slight; and it occurred also in the dog with heightened reflexes despite the increase in metabolism.

VI. ALCOHOL CHECKS

The validity of the work here presented is supported by the following alcohol checks. The calculated heat production and the theoretical oxygen consumption were estimated from the carbon dioxide production of the burning alcohol.

TABLE 4
Average of alcohol checks

NUMBER OF EXPERIMENT	DATE	R. Q.	PER CENT ERROR ON O ₂	CALORIES	
				Indirect	Direct
	<i>1991</i>				
84	January 24	0.671	-0.6	68.20	67.98
85	February 3	0.651	+2.4	68.50	67.04
86	February 8	0.650	+2.6	65.05	62.19
88	February 10	0.667	±0	43.32	41.45
89	March 2	0.658	+1.3	70.83	69.41
90	March 3	0.676	-1.3	34.54	38.21
		0.662	+0.7	350.44	346.28

TABLE 6
Dog XVIII

DATE	EXPERIMENT NUMBER	TIME	CALORIES				Urine N	H ₂ O	R. Q.	O ₂	CO ₂	BODY TEMPERATURE	LEUCINEMINIMUM	BEHAVIOR OF DOG	FOOD
			Protein	Non-protein	Indirect	Direct						Start	End		
1921															
Feb. 11	76A	10.50-12.50	10.94	9.69	0.82	15.13	0.2015	3.427	0.232	36.30	45.37	41.37	11.05	Quiet	Basal metabolism
Feb. 11	76B	2.15- 3.15	4.84	4.35	0.81	8.36	0.1183	11.29	14.44	12.57	36.57			Quiet	Morphine, 15 mgm. per kilogram, 2 injections at 1 and 1.40 p.m., 35 minutes before start
		3.15- 5.15	10.69	9.96	0.77	15.35	0.2366	3.3026	5.532	85.23	16.47	34.91	11.05		
										47.29	40.73				
Feb. 12	77	10.35-11.35	5.06	4.96	0.74	8.23	0.0922	2.4413	7.916	24.14	52.36	53	11.05	Quiet	Basal metabolism
		11.35-12.35	5.06	4.87	0.76	7.50	0.0922	2.4413	5.616	00.16	31.36	29		Quiet	
										32.24	30.83				
Feb. 17	78	2.18- 3.18	5.68	4.87	0.85	8.79	0.0852	2.2514	15.16	40.18	21.38	13	10.85	Quiet	Basal metabolism
		3.18- 4.18	5.84	5.40	0.79	7.77	0.0852	2.2515	6.617	91.19	28.37	65			
										34.31	37.49				
Feb. 18	79	11.09-12.09	5.37	4.36	0.90	6.37	0.1433	3.7910	9.414	73.13	65.36	25	10.80		Morphine, 15 mgm. per kilogram, 2 injections at 9.31 and 10.10 a.m., 1 hour before start
		12.09- 1.09	5.43	4.53	0.87	6.61	0.1433	3.7911	4.315	22.16	10				
		1.09- 2.09	5.43	4.59	0.86	6.37	0.1433	3.7911	5.915	38.15	86				
		2.09- 3.09	5.54	5.11	0.79	6.33	0.1433	3.7913	05.16	84.16	30.62	17	34.98		
										62.17	61.91				

Feb. 25	80A	11.32-12.32	5.82	5.12	0.83	5.87	0.104	2.76	14.36	17.12	17.04	37.45	37.36	10.65	Quiet	Basal metabolism
Feb. 25	80B	1.56- 2.56	5.20	4.02	0.94	5.86	0.144	3.82	9.89	13.71				10.65		Morphine, 15 mgm. per kilogram, 30 minutes before start. Rectal thermometer broken
		2.56- 3.56	5.29	4.77	0.81	6.24	0.144	3.82	11.96	15.78						
		3.56- 4.56	5.06	4.65	0.79	6.33	0.144	3.82	11.50	15.32						
									44.81							
Mar. 1	81	2.05- 3.05	5.01	4.85	0.75	9.18	0.154	4.08	11.72	15.80	17.30	37.46		10.50	Quiet	Morphine, 15 mgm. per kilogram, 45 minutes before the start
		3.05- 4.05	5.19	4.55	0.83	8.41	0.154	4.08	11.00	15.08	15.29					
		4.05- 5.05	5.40	5.22	0.75	7.99	0.154	4.08	12.95	17.03	15.27		35.41			
									47.91	47.86						

TABLE 5
Dog XVIII

DATE	EXPERIMENT NUMBER	TIME	CO ₂	O ₂	R. Q.	H ₂ O	Urine N	CALORIES				BODY TEMPERATURE		LEADING MINUTES	BEHAVIOR OF DOG	FOOD
								Protein	Non-protein	Indirect	Direct	Start	End			
1921			gm.	gm.		gm.	gm.							kgm.		
Feb. 11	76A	10.50-12.50	10.94	9.69	0.82	15.13	0.201	5.34	27.02	32.36	30.45	37.41	37.11	11.05	Quiet	Basal metabolism
Feb. 11	76B	2.15- 3.15	4.84	4.35	0.81	8.36	0.118	3.15	11.29	14.44	12.57	36.57		11.05	Quiet	Morphine, 15 mgm. per kilogram, 2 injections at 1 and 1.40 p.m., 35 minutes before start
		3.15- 5.15	10.69	9.96	0.77	15.35	0.236	6.30	26.55	32.85	28.16		34.91			
										47.29	40.73					
Feb. 12	77	10.35-11.35	5.06	4.96	0.74	8.23	0.092	2.44	13.79	16.24	14.52	36.53		11.05	Quiet	Basal metabolism
		11.35-12.35	5.06	4.87	0.76	7.50	0.092	2.44	13.56	16.00	16.31		36.29		Quiet	
										32.24	30.83					
Feb. 17	78	2.18- 3.18	5.68	4.87	0.85	8.79	0.085	2.25	14.15	16.40	18.21	38.13		10.85	Quiet	Basal metabolism
		3.18- 4.18	5.84	5.40	0.79	7.77	0.085	2.25	15.66	17.91	19.28		37.65			
										34.31	37.49					
Feb. 18	79	11.09-12.09	5.37	4.36	0.90	6.37	0.143	3.79	10.94	14.73	13.65	36.25		10.80		Morphine, 15 mgm. per kilogram, 2 injections at 9.31 and 10.10 a.m., 1 hour before start
		12.09- 1.09	5.43	4.53	0.87	6.61	0.143	3.79	11.43	15.22	16.10					
		1.09- 2.09	5.43	4.59	0.86	6.37	0.143	3.79	11.59	15.38	15.86					
		2.09- 3.09	5.54	5.11	0.79	6.33	0.143	3.79	13.05	16.84	16.30		34.98			
										62.17	61.91					

Feb. 25	80A	11.32-12.32	5.82	5.12	0.83	5.87	0.104	2.76	14.36	17.12	17.04	37.45	37.36	10.65	Quiet	Basal metabolism
Feb. 25	80B	1.56- 2.56	5.20	4.02	0.94	5.86	0.144	3.82	9.89	13.71				10.65	Quiet	Morphine, 15 mgm. per kilogram, 30 minutes before start. Rectal thermometer broken
		2.56- 3.56	5.29	4.77	0.81	6.24	0.144	3.82	11.96	15.78						
		3.56- 4.56	5.06	4.65	0.79	6.33	0.144	3.82	11.50	15.32						
									44.81							
Mar. 1	81	2.05- 3.05	5.01	4.85	0.75	9.18	0.154	4.08	11.72	15.80	17.30	37.46		10.50	Quiet	Morphine, 15 mgm. per kilogram, 45 minutes before the start
		3.05- 4.05	5.19	4.55	0.83	8.41	0.154	4.08	11.00	15.08	15.29					
		4.05- 5.05	5.40	5.22	0.75	7.99	0.154	4.08	12.95	17.03	15.27		35.41			
									47.91	47.86						

TABLE 6
Dog XIX

DATE	EXPERIMENT NUMBER	TIME	CO ₂	O ₂	R. Q.	H ₂ O	Urine N	CALORIES				BODY TEMPERATURE		WEIGHT MORNING	BEHAVIOR OF DOG	FOOD
			gm.	gm.		gm.	gm.	Protein	Non-protein	Indirect	Direct	Start	End	kgm.		
Feb. 4	55A	10.45-11.45	5.58	5.17	0.78	5.78	0.092	2.44	14.69	17.13	15.96	37.95		9.35	Quiet	Basal metabolism
		11.45-12.45	5.70	5.26	0.79	5.78	0.092	2.44	15.17	17.45	16.75	37.79			Quiet	
									34.58	32.71						
Feb. 4	55B	2.14-3.14	6.17	4.75	0.94	7.24	0.092	2.44	13.92	16.36	17.05	36.40		9.35	Restless	Morphine, 12 mgm. per kilogram at 1 p.m., 1½ hours before start
		3.14-4.14	6.66	5.54	0.87	7.54	0.092	2.44	16.43	18.87	16.50	35.54			Restless	
									35.23	33.55						
Feb. 15	57	2.27-3.27	5.87	5.23	0.82	6.18	0.096	2.54	14.93	17.47	18.09	38.34	38.40	9.15	Quiet	Basal metabolism
Feb. 16	58	10.55-11.55	6.61	5.67	0.85	8.09	0.122	3.23	15.82	19.05	17.55	37.55		9.20	Occasional movements	Morphine, 20 mgm. per kilogram given 50 minutes before start
		11.55-12.55	7.45	6.01	0.90	7.81		3.23	17.26	20.49	17.22				Moving 6 minutes	
		12.55-1.55	7.66	6.39	0.87	7.97		3.23	18.41	21.64	20.06	35.92			Very restless	
Feb. 23	59	1.36-2.36	6.39	5.23	0.89	7.76	0.162	4.29	13.37	17.66	18.84	38.09		9.65	Quiet	Basal metabolism
		2.36-3.36	6.05	5.33	0.83	7.23		13.43	17.72	17.61		38.15			Quiet	
									35.38	36.45						

Feb. 24	60	2.40- 3.40	7.43	6.34	0.85	7.78	0.13	3.53	17.81	21.34	20.80	36.50	9.55	Moving 4 minutes Moving 3 minutes	Morphine, 15 mgm. per kilogram at 1.30 p.m. Ether 10 minutes, then chloroform until corneal reflex disappeared
		3.40- 4.40	7.43	6.46	0.84	7.73	0.13	3.53	18.13	21.66	21.87	36.46			
										43.00	42.67				
Feb. 28	61	12.02- 1.02	6.99	5.92	0.86	10.09	0.17	9.4.74	15.12	19.86	17.88	37.45	9.60	Moving 1 minute Occasional movements Quiet Moving 1 minute every 10 minutes	Morphine, 15 mgm. per kilogram at 11 a.m. Ether 5 minutes until corneal reflex disappeared
		1.02- 2.02	6.44	5.49	0.85	8.25	0.17	9.4.74	13.62	18.36	17.90				
		2.02- 3.02	6.09	5.48	0.81	8.73	0.17	9.4.74	13.38	18.12	17.36				
		3.02- 4.02	6.16	5.63	0.80	9.14	0.17	9.4.74	13.82	18.56	17.38	30.05			
										74.90	70.52				

Although these alcohol checks are by no means perfect, it is evident that in general the results obtained by the calorimeter must have been trustworthy during the month of February when the experiments showing the influence of morphine upon the metabolism of dogs were accomplished.

VII. SUMMARY

1. Two dogs reacted differently to doses of between 12 and 20 mgm. of morphine per kilogram of body weight.

2. Dog XVIII, which remained absolutely quiet in morphine sleep, showed during the second hour after treatment an average fall in the heat production of 11 per cent below the basal level, for the third hour 6 per cent, for the fourth hour 4 per cent. The average reduction for all the periods was 6.2 per cent. The respiratory quotients were unchanged by administration of morphine.

3. In a typical experiment upon this dog the heat production was 0.6 calorie per hour less than the basal value of 16.6 calories, but the animal lost from its body to the calorimeter 6 calories per hour, or 32 per cent, more than it produced. The decrease in heat production cannot therefore be the cause of the fall in body temperature. There was no abnormal condition in the division of heat loss as between radiation and conduction and the evaporation of water.

4. Dog XIX manifested increased irritability with heightened reflexes after administering the drug. The basal metabolism increased by an average of 10 per cent. The maximum increase was 23 per cent after administering morphine, ether and chloroform. The respiratory quotients were higher after giving morphine to this dog, perhaps due to the preference of the active muscle for carbohydrate.

5. The increase in the metabolism of this irritable dog did not prevent a loss of body heat and consequent fall in body temperature after giving morphine. The pathways for the distribution of the heat loss were relatively unaltered.

6. In one experiment when morphine, ether and chloroform were given together there was no change in the body temperature.

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ANIMAL CALORIMETRY.

TWENTY-SECOND PAPER.

THE PRODUCTION OF FAT FROM PROTEIN.

By H. V. ATKINSON, DAVID RAPPORT, AND GRAHAM LUSK.

WITH THE TECHNICAL ASSISTANCE OF G. F. SODERSTROM AND
JAMES EVENDEN.

(From the Physiological Laboratory of Cornell University Medical College,
New York City.)

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In the second paper of this series Williams, Riche, and Lusk (1) described experiments which showed the hourly metabolism of a dog after giving 1,200 gm. of meat. The dog weighed 13.5 kilos and was maintained by administering 1,200 and 700 gm. of meat on alternate days. When given the larger quantity of meat, which contained about 1,200 calories, the heat production was about 800 calories daily, the dog resting quietly. The protein content of the meat was the equivalent of 900 calories. It follows that the protein ingested was alone more than sufficient for the dog's needs. However, when 700 gm. of meat were given the heat production of the resting quiet dog was about 700 calories daily, the ingested meat contained the same number of calories, while the protein element contained only 525 calories. Under these latter conditions one would not expect any permanent retention of glycogen derived from the protein metabolism of this dog during a day of ordinary activity following the administration of 700 gm. of meat.

The conditions were therefore favorable for the deposit of glycogen in the liver following the administration of 1,200 gm. of meat. As a matter of fact, during a period of 14 hours after the administration of this large amount of meat there was much less carbon eliminated in the respiration than corresponded to the protein metabolism of the time as measured by the excretion of

nitrogen in the urine. That this carbon was retained in the form of glycogen was proved by the fact that the quantity of oxygen absorbed agreed with this hypothesis, and that the heat calculated on the basis of a retention of glycogen agreed with the heat as measured by the calorimeter.

The Work of Atkinson and Lusk.

Fat Formation.—Atkinson and Lusk (2) performed a long series of experiments with the object of discovering the quality of the material retained when, after giving meat in large quantity to a dog, the amount of protein metabolism was in excess of the fuel needed for the heat production of the time.

A résumé of these experiments is given in Table I.

It will be remembered that when the protein of meat is oxidized in the body the respiratory quotient is 0.801.

It is evident from the table that in ten out of twelve experiments, after giving meat amounting to between 700 and 1,300 gm. daily, the respiratory quotients varied between 0.787 and 0.808, as appears below:

Experiment No..	31	48	54	51	47	46	55	30	34	32
R. Q.....	0.787	0.793	0.794	0.795	0.795	0.796	0.797	0.800	0.800	0.808
R. Q. of deposit..	0.960	0.860	0.860		0.840		0.830	0.830	0.830	0.770

In Experiments 51 and 46 there was no retention of protein carbon, whereas in six of the experiments the retained carbon was held in such a form that, had it been oxidized, it would have yielded respiratory quotients of between 0.83 and 0.86, which indicates the retention of a pabulum containing only about half of its calories in fat and half in carbohydrate. By weight this would indicate the retention of approximately 1 gm. of fat to every 2 gm. of glycogen.

Only after the ingestion of meat in very large quantities—1,100 and 1,300 gm.—was there evidence of the conversion of protein into fat as the dominant feature of the process. This appears below:

Experiment No.....	33a	33b	56
R. Q.....	0.831	0.843	0.826
R. Q. of deposit.....	0.680	0.490	0.710

As the respiratory quotient of fat is 0.707, the above results warranted the conclusion that in the case of excessive ingestion of meat by a dog the retained pabulum might be laid down as fat when the circumstances were favorable. It was noted that it was very difficult to induce the dog to take meat in these very large quantities.

During the period of experimentation twelve alcohol checks were made. The average of all the respiratory quotients was 0.668 (theory 0.667) and the heat recovered was 0.3 per cent greater than the heat calculated to be obtainable from the combustion of the alcohol.

The extent of the hourly retention of carbon calculated from the protein metabolism (measured by the urinary nitrogen) and the CO_2 output of the period bear no relation to the total heat production, as appears in the following tabulation:

Experiment No..	55	47	34	30	48	54	56	33a	31	32
Protein C retained, gm.....	0.91	0.77	0.70	0.66	0.61	0.59	0.59	0.56	0.48	0.32
Calories of metabolism.....	32.00	29.90	34.00	31.50	29.40	31.10	31.60	31.70	34.30	34.90

It is well known that the deposition of glycogen does not increase the heat production. In Experiments 33a and 56, in which fat appeared to be the sole material deposited, the heat production was no higher than in Experiments 55, 47, 30, 48, 54, and 31, when fat and glycogen were laid down in about equal caloric equivalents.

It is therefore apparent that *the specific dynamic action of protein is not due to the formation or deposition of synthetically formed glycogen or fat.*

Basal Metabolism and "Deposit Protein."—"Deposit protein" is that quantity of protein which is held in the body after excessive protein ingestion, and which is gradually eliminated from the cells in which it is stored upon the cessation of a high protein diet. Historically it is the same as Voit's "circulating protein." Benedict, Miles, Roth, and Smith (3) were the first to associate the loss of "deposit protein"—which they called "surplus cellular nitrogen"—with a reduction in the total metabolism of men.

TABLE I.
Effect of Meat Ingestion on Hourly Metabolism. Series I. Dog XVIII.

Experiment No.	Date.	Food.	Num-ber of hours.	Urine N.	R. Q.	Calories.		C deposited.	R. Q. of deposited material.	Hours after food.
						Indirect.	Direct.			
	1919			gm.				gm.		
27	Feb. 6	Basal.	2	0.15	0.840	15.92	16.08			
30	" 18	Meat, 800 gm.	3	1.46	0.800	31.47	32.75	+0.63	0.83	(Weight = 11.24 kg.)
31	" 19	" 900 "	3	1.47	0.787	34.33	34.14	+0.48	0.96	4, 5, 6
32	" 20	" 1,000 "	4	1.46	0.808	34.90	35.87	+0.32	0.77	4, 5, 6
33	" 21	" 1,100 "	2a	1.45	0.831	31.65	31.36	+0.56	0.68	4, 5, 6, 7
			2b	1.45	0.843	35.28	34.54	+0.25	0.49	4, 5, 6, 7
	Feb. 22	Meat, 700 gm.								
	" 23	" 700 "								
34	" 24	" 1,080 " *	2	1.57	0.800	34.00	34.12	+0.70	0.83	4, 5
35	" 26	Basal.	3	0.27	0.820	19.74	19.59			
36	" 27	" "	3	0.20	0.830	18.25	17.16			
37	" 28	" "	2	0.17	0.850	17.30	16.95			
38	Mar. 1	" "	2	0.15	0.820	18.21	(18.21)			
39	" 3	" "	3	0.15	0.850	17.57	17.22			
43	" 12	" "	2	0.15	0.810	17.08	16.99			(Weight = 11.50 kg.)

46	Mar. 17	Meat, 1,200 gm.	3	1.02	0.796	26.57	28.10	0		5, 6, 7 after 1 day's fast.
47	" 18	" 800 "	3	1.44	0.785	29.90	30.77	+0.77	0.84	5, 6, 7
48	" 19	" 800 "	4	1.35	0.793	29.37	30.27	+0.61	0.86	5 to 8
49	" 22	Basal.	2	0.23	0.790	17.72	17.54			
50	" 24	"	2	0.16	0.840	17.26	16.87			
51	" 28	Meat, 800 gm.	4	1.02	0.795	27.04	27.52			5 to 8 after 4 days' fast.
54	Apr. 15	" 800 "	4	1.41	0.794	31.07	30.57	+0.59	0.86	5 to 8
55	" 16	" 1,000 "	4	1.58	0.797	31.97	31.98	+0.91	0.83	5 to 8
56	" 19	" 1,300 "	4	1.47	0.826	31.62	33.25	+0.59	0.71	5 to 8 after 1 day's fast.
Total						568.22	571.85			

* Standard diet at 5 p.m. and thereafter daily until Mar. 15.

TABLE II—The Effect of Meat Inge

Date.	Experiment No.	Time.	CO ₂	O ₂	R. Q.	H ₂ O	Urine N.	Non-protein.			Protein.	Net prot.
								CO ₂	O ₂	R. Q.		
1920												
Mar. 26	80	12.24— 1.28	6.70	7.34	0.664	4.84						
		1.28— 2.28	6.16	6.70	0.669	4.24						
					0.667							
Apr. 14	68 Dog XVIII	12.48— 1.48	4.93	4.17	0.860	7.48	0.103			0.875	2.73	II
		1.48— 2.48	4.80	4.28	0.816	6.76	0.103			0.819	2.73	II
Apr. 17	70 Dog XVIII	12.40— 1.40	10.10	5.14	0.842	11.83	1.440	-3.36	-3.45	0.708	38.17	-II
		1.40— 2.40	10.45	5.32	0.845	11.94	1.440	-3.01	-3.18	0.688	38.17	-M
		2.40— 3.40	10.56	5.38	0.845	10.69	1.440	-2.90	-3.08	0.685	38.17	-M
					0.844					0.694		
Apr. 19	81	3.04— 4.04	6.45	7.03	0.667	4.57						
		4.04— 4.44	4.46	4.80	0.676	3.06						
					0.670							
1922												
Mar. 6	141	1.41— 2.41	8.17	8.95	0.664	6.14						
		2.41— 3.41	8.09	8.93	0.659	5.87						
		3.41— 4.41	8.01	8.75	0.666	5.78						
					0.663							
Mar. 8	142	11.26—12.26	8.33	8.98	0.674	6.12						
		12.26— 1.26	8.27	9.21	0.653	5.94						
					0.664							
Mar. 8	75 Dog XIX	2.50— 3.50	11.54	10.36	0.810	13.86	1.80	-5.32	-4.88	0.786	47.80	-I
		3.50— 4.50	11.73	9.97	0.856	13.19	1.80	-5.13	-5.27	0.708	47.80	-I
					0.833					0.749		
Mar. 11	144	10.21—11.21	7.75	8.53	0.661	5.97						
		11.21—12.21	7.66	8.41	0.662	5.65						
					0.662							

* Calorimeter cold.

Early Metabolism. Series II.

Direct.	Body temperature.		Morn- ing weight.	Behavior of dog.	Food.
	Start.	End.			
			kg.		
24.50					
21.95					
46.45					
12.76	37.81		8.57	Quiet.	Basal metabolism:
14.31		37.45		"	
27.07					
27.52				Quiet.	1,000 gm. of meat at 8.33 a.m. 3rd day of same
29.07				"	diet. Also 100 gm. of biscuit meal at 5 p.m. for
28.73		38.48		"	previous 2 days.
85.32					
23.47					
16.12					
39.59					
30.24					
29.76					
29.95					
89.95					
32.66					
31.75					
64.41					
30.89	38.72			Quiet.	1,000 gm. of meat at 9 a.m. 3rd day of same diet.
33.42		38.65		"	Standard diet also given constantly at 5 p.m.
64.31					
26.65*					
27.78					
54.43					

Date.	Experiment No.	Time.	CO ₂	O ₂	R. Q.	H ₂ O	Urine N.	Non-protein.			Protein.	Protein.
								CO ₂	O ₂	R. Q.		
			gm.	gm.		gm.	gm.	gm.	gm.			
1928												
Mar. 11	77	1.54- 2.54	12.85	10.92	0.856	22.65	1.803	-4.01	-4.32	0.675		
		2.54- 3.54	13.40	11.65	0.837	19.85	1.803	-3.46	-3.59	0.701		
					0.846					0.687		
Mar. 15	145	11.34-12.34	7.63	8.30	0.669	5.67						
		12.34- 1.34	7.31	8.16	0.652	5.42						
					0.660							

In Table I it will be noted that the basal metabolism of a dog maintained upon the ordinary "standard diet" (meat, 100 gm.; biscuit meal, 100 gm.; lard, 20 to 30 gm.) was 16 calories per hour. After 8 days of meat ingestion as the sole diet, administration of the "standard diet" was resumed. 18 hours after the second administration of the "standard diet" the basal metabolism was 19.7 calories and then on successive days was measured as being 18.3, 17.3, 18.2, and 17.6 calories. Even after 2½ weeks the basal metabolism was 17.08 calories, showing a persistently higher level than had obtained before the ingestion of meat.

The bodily condition is always a factor to be considered in the determination of basal metabolism. The condition of muscular strength, accompanied by the addition of an "improvement quota" of protein (4) to the cells of the body, results also in a higher metabolism in the dog (5) and in man (6). It is possible that a lesser amount of "deposit protein" and of "improvement protein" may be in part responsible for the lower basal metabolism of women, first pointed out by Gephart and Du Bois (7). Thus the recent experiments of Blunt and Bauer (8) show that under-nutrition does not play a large part in reducing the metabolism of women.

The Experiments of Rapport and Lusk.

The problem of the production of fat from protein seemed of sufficient significance to endeavor to follow the same with the

cluded.

Direct.	Body temperature.		Morning weight.	Behavior of dog.	Food.
	Start.	End.			
			kg.		
36.47	39.04		13.0	Quiet.	Meat 1,000 gm. at 9 a.m. 6th day of same diet at 9 a.m., with standard diet also daily at 5 p.m.
36.44		38.76		"	
72.91					
26.93					
26.65					
53.58					

greatest care as to the accuracy of the determination of the individual respiratory quotients after meat ingestion.

An additional procedure was added in this series. The standard diet, containing 70 gm. of starch, was given every evening at 5 p.m. in order to charge the glycogen reservoirs of the body. The meat was given early in the morning. The complete data are to be found in Table II. The accuracy of the experiments may be gauged from the following figures:

Date.		R. Q.	R. Q. of retained material.
1920			
Mar. 26	Alcohol check.	0.667	0.694
Apr. 17	Meat ingestion.	0.844	
" 19	Alcohol check.	0.670	
1921			
Mar. 6	" "	0.663	0.749
" 8	" "	0.664	
a.m.	" "	0.664	
p.m.	Meat ingestion.	0.833	0.687
Mar. 11	Alcohol check.	0.662	
a.m.	Meat ingestion.	0.846	
p.m.	Alcohol check.	0.660	

If protein is converted into fat two conditions must be fulfilled: (a) the R. Q. must be higher than that of protein itself

and (b) there must be a retention of protein carbon. The urinary nitrogen is usually higher in the dog when the animal is catheterized hourly (1) than it is when it accumulates in the bladder during a calorimeter period, and the true index of protein metabolism is accounted to be the level to which the urinary nitrogen rises when the urine is fractionated hourly on a day that the dog is given the same diet but is not in the calorimeter.

The method of calculation of the 5th hour after giving 1,000 gm. of meat to Dog XVIII will suffice as a guide to all the experiments.

Experiment 68.

Urinary N = 1.44 gm.

	CO ₂ gm.	O ₂ gm.	Calories.
Equivalent of 1.44 gm. of N.....	13.46	12.17	38.17
Found in respiration.....	10.10	8.72	
	3.36	3.45	11.32

Calories indirect..... 26.85

R. Q. of deposit = 0.708

Value of fat deposited = 11.32 calories

Calories (indirect) = 26.85

Calories (direct) = 27.52

C retained = 0.92 gm. $\left\{ \begin{array}{l} = 1.2 \text{ gm. of fat} \\ = 2.3 \text{ gm. of glucose (8.63 calories)} \end{array} \right.$

Calories if C had been retained as glycogen = 29.54

The respiratory quotients and the heat directly measured confirm the conception that fat and not glycogen was the form in which the carbon was deposited.

If one makes use of this method of calculation for the average hourly heat production for the series of three experiments, one may construct Table III.

It is evident that, computed on the oxygen absorption by the method of indirect calorimetry already outlined, the calculated heat production is almost exactly the same as it is when the computation is based upon the hypothesis that the carbon retained is laid down in the form of fat (1 gm. of C retained as fat = 12.31 calories).

The agreement between direct and indirect calorimetry is not as close as one would wish, though in this regard the alcohol checks agree on the average within 1 per cent. The calories as calculated are 3.8 per cent less than the calories found. However, if the carbon retention is assumed to take the form of glycogen, then the calculated heat would be 6.3 per cent higher than the amount directly measured. The findings, therefore, favor the idea of the retention of a pabulum in the form of fat.

TABLE III.

Direct and Indirect Calorimetry in Hourly Periods after the Ingestion of 1,000 Gm. of Meat.

	Experiment No.	Urine N.	Protein C to body.	Calories.			
				Direct.	Indirect.	C ^e deposited as fat.	C deposited as carbohydrate.
		gm.					
Dog XVIII..	68	1.44	0.84	28.44	27.55	27.83	30.30
Dog XIX....	75	1.80	1.40	32.16	30.97	30.51	34.57
	77	1.80	1.02	36.46	34.83	35.25	38.29
Total.....				97.06	93.35	93.59	103.16

Here, as in the first series of experiments, the height of the metabolism is not proportional to the quantity of protein carbon retained. In Experiment 77, high humidity in the calorimeter probably produced increased respiratory activity and in consequence increased metabolism. The older literature has been elsewhere reviewed (9), but these experiments, by a new method, add another link to the chain of evidence that protein may be converted into fat. It must be remembered, however, that the conditions were exceptional, in that the animals were maintained upon a nutritive plane which would fill the glycogen reservoirs, were given meat up to the limit of their willingness to consume it, and were kept in absolute rest in a calorimeter at an environmental temperature of 25°C. Under these circumstances fragments of protein metabolism, which would ordinarily have been oxidized or converted into glucose and laid down as glycogen, found no other pathway open than conversion into fat. Under a natural diet these conditions would not exist.

SUMMARY.

1. When the glycogen reservoirs of the body are low the ingestion of meat in large quantity results in the deposition of glycogen.

2. The continued ingestion of much meat brings about the retention in the body of a pabulum consisting partly of glycogen and partly of fat. Only when meat in very great excess is given is fat alone retained.

3. When a carbohydrate-containing meal is given in the evening and 1,000 gm. of meat in the morning, then during the height of protein digestion the respiratory quotient indicates a production of fat from protein.

4. Following the prolonged ingestion of meat in large amounts, which induces the retention of "deposit protein," the basal metabolism may rise from a former level of 16 calories per hour to one of 19.7, an increase of 23 per cent, from which level it slowly falls with the gradual elimination of "deposit protein."

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THE INFLUENCE OF MEAT UPON PHYSICAL EFFICIENCY

S. H. BASSETT, EVELYN HOLT AND F. O. SANTOS

*From the Physiological Laboratory, Cornell University Medical College,
New York City*

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The mystery regarding the significance of meat in the dietary is yet to be clarified. In the following experiments there were four different periods of one week in length. During the first week the usual normal diet was taken by each individual. During the second week a luncheon containing 300 grams of beef was served, with bread, butter and boiled potatoes, in the laboratory. This quantity of meat is the amount which was contained in the daily war ration of the French and Italian soldier. During the third week little or no meat was taken, and during the fourth week the same procedure was followed as in the second week. The four individuals engaged in this work analyzed their urines daily for nitrogen; all wore pedometers for measuring the number of their daily movements. They also were instructed to walk a given distance both morning and late afternoon on their way to and from the college, striving to accomplish the walk in the shortest time possible. On completing the walk the pulse was counted and then the time noted until the pulse rate became normal once more. This has been suggested by the work of Lewis, Cotton and Rapport (1) as a test of physical fitness.

The subjects were an instructor in the laboratory (R.), a Philippino (S.) working for a higher degree, a man (B.) and a woman (H.) student. The first named was in perfect physical condition after a summer in the Maine woods; the fourth was fond of long walks and tennis in which she indulged during the experimental periods. The other two subjects were in good general health. The basal metabolism of S., who weighed 40 kgm., was 41 calories per square meter of surface, the normal value.

The observations may be thus summarized:

TABLE 1

Subject B., weight 64 kgm.

	FIRST WEEK		SECOND WEEK		THIRD WEEK		FOURTH WEEK	
	Ordinary diet		High protein		Low protein		High protein	
Average number of steps per day.....	14,253		12,636		14,840		13,616	
Urine N (average) grams..	13.14		17.44		8.68		18.34	
Maximum-minimum....	14.08-11.31		18.57-17.12		11.37-7.53		21.67-15.48	
	a. m.	p. m.	a. m.	p. m.	a. m.	p. m.	a. m.	p. m.
Time in minutes of test walk.....	11.43	12.4	12.7	14.5	14.0	17.0	16.5	15.0
Time in minutes to make 1000 steps.....	8.51	8.50	8.80	9.70	9.33	9.50	9.45	9.38
Pulse:								
Before exercise.....	71.0	71.0	73.0	75.0	73.0	74.0	77.0	79.0
End of exercise.....	86.0	85.0	102.0	101.0	100.0	93.0	107.0	102.0
After 3 minutes.....					87.0	80.0	91.0	88.0
After 5 minutes.....	72.0	75.0	86.0	79.0	84.0	77.0	88.0	84.0

TABLE 2

Subject H., weight 58 kgm.

	FIRST WEEK		SECOND WEEK		THIRD WEEK		FOURTH WEEK	
	Ordinary diet		High protein		Low protein		High protein	
Average number of steps per day.....	21,520		21,503		19,691		20,880	
Urine N (average) grams..	9.64		14.72		8.02		16.91	
Maximum-minimum.....	10.43-8.80		17.06-13.34		8.78-6.86		19.38-15.83	
	a. m.	p. m.	a. m.	p. m.	a. m.	p. m.	a. m.	p. m.
Time in minutes of test walk.....	26.0	27.0	26.0	27.0	26.0	27.5	26.0	27.5
Time in minutes to make 1000 steps.....	7.0	7.3	7.0	7.3	7.0	7.4	7.0	7.4
Pulse:								
End of exercise.....	112.0	107.0	120.0	105.0	121.0	117.0	113.0	114.0
After 4 minutes.....	78.0	81.0	81.0	83.0	82.0	82.0	81.0	78.0
After 5 minutes.....		74.0		81.0		75.0		75.0

TABLE 3

Subject R., weight, 58 kgm.

	FIRST WEEK	SECOND WEEK	THIRD WEEK		FOURTH WEEK	
	Ordinary diet	High protein	Low protein		High protein	
Average number of steps per day.....	14,980	13,145	16,415		14,965	
Urine N (average) grams..	12.5	18.9	12.3		18.9	
Maximum-minimum.....	14.9-10.1	19.6-18.0	14.3-10.1		19.7-17.6	
	a. m.	a. m.	a. m.	p. m.	a. m.	p. m.
Time in minutes of test walk.....	20.9	22.0	21.8	19.1	21.9	19.3
Time in minutes to make 1000 steps.....	9.03	9.14	9.04	9.48	9.07	9.75
Pulse:						
Start of exercise.....	70.0	69.0	69.0	72.0	70.0	71.0
End of exercise.....	96.4	96.0	91.0	95.0	94.0	101.0
Time in minutes of re-turn to normal.....	1.17	1.25	1.37	1.82	1.55	2.05

TABLE 4

Subject S., weight 40 kgm.

	FIRST WEEK		SECOND WEEK		THIRD WEEK		FOURTH WEEK	
	Ordinary diet		High protein		Low protein		High protein	
Average number of steps per day.....	13,902		14,552		15,695		14,808	
Urine N (average) grams	12.36		15.78		7.89		15.77	
Maximum-minimum.....	14.07-9.34		18.65-13.44		8.99-7.31		16.88-13.15	
	a. m.	p. m.	a. m.	p. m.	a. m.	p. m.	a. m.	p. m.
Time in minutes of test walk.....	28.2	28.5	28.0	28.5	27.3	27.8	27.4	27.5
Time in minutes to make 1000 steps.....	9.24	9.34	9.17	9.34	8.99	9.18	9.04	9.13
Pulse:								
Before exercise.....	85.0	85.0	84.0	85.0	80.0	81.0	80.0	81.0
End of minute.....	111.0	113.0	114.0	110.0	120.0	112.0	121.0	119.0
After 3 minutes.....	97.0	97.0	94.0	98.0	85.0	88.0	79.0	88.0
After 5 minutes.....	90.0	95.0	87.0	90.0		80.0		80.0

SUMMARY

The results show that the presence or absence of meat from the dietary, during periods as long as one week, has no demonstrable effect upon the capacity of doing an amount of work so graded as to reach the limit of the physical capacity during a short period of time. This accords with the doctrine of Chittenden (2). There was a distinct and uniformly present sense of sleepiness for 2 or 3 hours during the afternoon period following the ingestion of 300 grams of meat. Removal of meat from the dietary for a period of one week did not diminish the sense of well-being in the individuals investigated. The well-nigh universal opinion that meat ingestion is important for the maintenance of physical strength is not to be disregarded, but the experimental evidence in favor of this conception has yet to be produced.

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ON THE MECHANISM OF ABSORPTION FROM THE INTESTINE

SAMUEL GOLDSCHMIDT

*From the Physiological Laboratory, Cornell University Medical College,
New York City*

In the historical (1), (2) development of the conceptions of the mechanism of absorption from the intestinal tract, as well as absorption in other parts of the organism, it is of interest to note that the controversy has from the start centered around physical or physico-chemical theories as a basic cause. As the principles of physical chemistry were developed, the new points of view were brought to bear upon this ever elusive physiological phenomenon. When one considers the subject intensively one gains more and more the impression that the final analysis must lie in these realms; that it awaits only the development of the fundamental subject of physical chemistry and the persistent application of its principles to biological sciences.

There will ever be, from the very complex nature of the process, points which will seem fundamentally unexplainable, or which one may assign to "vital" forces bound up with the living cell protoplasm. However, the latter course hardly seems justifiable. Call them what we will, "vital" processes must never be relegated to a Pandora's box where hope is securely confined. As new physical or chemical principles are evolved, there can be no danger, and perhaps profit will accrue from examining, from time to time, these "vital" activities in the newer light.

In considering the intestinal wall as a membrane, subject to the principles and laws of such structures as we know them in physical chemistry (3), it is important not to overlook the fact that the functioning of this membrane is intimately associated with a complicated anatomical structure within the intestinal walls. The maintenance of the protoplasmic membrane in its normal state is, without doubt, essential to the absorptive processes as a whole. On the other hand, the inner structure is of prime importance in a consideration of the variations in the behavior of this membrane from those of purely isolated physico-chemical systems. By this statement is meant not a peculiar structural

arrangement of relatively permeable and impermeable phases of the cell itself, as suggested by Robertson (4), but in a broader sense every integral portion of the intestinal tissue.

Apart from the possibility of alterations on or within the surface layer or membrane of the intestine, therefore, equally important are the arrangement and the distribution of the absorbing vessels, and the quantitative and qualitative character of the fluid contained therein. As an illustration Heidenhain (5) points out that the absorption of fluid and dissolved substances, by the blood capillaries, for the most part, may be easily explained anatomically. The capillaries lie at the periphery of the villi, close beneath the epithelium; in fact, a slight shortening of a villus brings the vessels so close together that they almost touch. These facts are purely anatomical, but they may have a decided influence upon the path and even the mechanism of uptake of the absorbed products of digestion. For, as Heidenhain states, because of the higher osmotic concentration of the blood, which in spite of the large amount of fluid which passes into it is not greatly diluted, due to the great speed of the change of that fluid in the capillaries, the fluid and in great measure the dissolved substances, coming first in contact with this system, are carried away by it. The lymph stream, on the other hand, in addition to its less favorable position, is of a lower concentration and is as well a much more slowly moving stream.

To carry the illustration still further, Reid (6), (7), (8), (9) states that although there is no evidence of specific absorptive nerve fibers, nevertheless excitation of the mesenteric nerve by production of concomitant vasoconstriction or, indeed, any decrease in the blood supply to the intestine, i.e., blood-letting, may affect the absorptive process. It is also found that drugs which cause a general vasoconstriction, as adrenalin (10), or a more or less localized constriction affecting the intestinal vessels, i.e., pituitrin (11), decrease absorption. Hyperemia, on the other hand, may facilitate the process (12), (13).

Of importance also is the possible effect of various mechanical pressure forces which may exert themselves upon the intestinal structure, either from a mechanism inherent in the tissue itself or from without. Hamburger (14), (15), (16), in recent times, has emphasized the part played by intra-intestinal pressure in its absorptive action. The question, however, is an old one. Lieberkühn (1745) (17) discussed the action of peristalsis as an aid to absorption by the villi.

In the above connection it may be well to point out a property possessed by the villi, which may be of possible assistance to intestinal

absorption. Brücke (18) observed that the villi contained smooth muscle fibers in their long axis, the function of which is to cause by their contraction a shortening of the villi.¹ The anatomical presence of these muscle fibers and the demonstration of movements of the villi have found ample confirmation, although with slight modifications as to the character and distribution of the musculature and the form of the villus movement (5), (20), (21).

Both Lieberkühn and Brücke believed that they had observed openings into the villi.² Lieberkühn formulated the hypothesis that peristaltic movement presses fluid and solids into the openings of the villi whence they are taken up by the blood vessels. According to Brücke's conception, the villi act like suction pumps in their movement, thus causing fluids and particles not too large to pass into the openings to the central lymph duct. The action is a sort of filtration through a filter whose pores are wide enough so that undissolved bodies, i.e., small fat globules, can pass through into the lymph (22). The validity of the presence of openings into the villi has been questioned (1, p. 432), and it is generally believed today that particles do not normally pass through the intestinal wall. However, it must be pointed out that many investigators have claimed to have demonstrated that small insoluble bodies may pass by the intestinal route (23), (24), (25), (26).

That the movement of the villi exerts a rôle in absorption is still held by some experimenters (21), (29), and it would seem that tentatively, at least, it must be considered as a possible modifying influence. Cohnheim (27) holds that Brücke's theory cannot stand as a general statement of the intestinal mechanism, for the reason that in a Holothurian, which does not possess villi, absorption can occur when the intestine filled with sea-water is suspended in the same medium. Reid (8) has also shown that absorption takes place when the mesenteric lymph vessels are bound off, which is apparently contrary to the belief of Brücke that the path of uptake is into the central lymph space of the villus. Höber (28), however, has defended Brücke against Reid's attack by pointing out that, although the Holothurian lacks villi, it does possess an intestinal smooth muscle mechanism which can exert intra-intestinal pressure. In addition, the villi may still be the portal of entry, although the lymph vessels are tied off, if one assumes,

¹ Lacauchie (1853) (19) observed the movement of the villi but did not describe the muscle fibers.

² For a full discussion the reader is referred to Longet (1).

as did Friedenthal (29), that the substances, after entering the central lymph space, may then pass by diffusion into the blood stream.

If, therefore, one considers what has been said above, it is obvious that the insistence upon a normal functioning of the whole structure in its many parts, insofar as they can cause, modify or aid the absorptive process, is no more of an admission of its "vital" character than that any physical structure should break down as a whole due to a failure of one of its parts. In other words, we must consider these unique structures as integral parts of the mechanism. The influence of every possible factor concerned must be examined in order to evolve a satisfactory explanation of the intestinal mechanism of absorption. Hence it is not at all surprising that when an investigator has focused his attention upon one factor only, that single point of view has failed to explain the phenomenon. To be sure, the determination of the effect of each part may be best made by exclusion of that part or of all other interfering influences, but in the problem at hand this method presents difficulties. These remarks are especially pertinent when, as in the question under discussion, we have to make comparisons with a physico-chemical process in which exact imitation of conditions is not possible.

A detailed historical discussion of the entire subject at hand cannot be presented within the limits of this review. Nevertheless, an attempt will be made at least to refer to each explanation (founded on experimental evidence) and theory that has been advanced, of which the following is a compilation:

1. Absorption through orifices in the blood vessels, especially the veins, in the intestinal wall (Hippocrates and Galen (30)).
2. Imbibition, of the nature of water absorption by a sponge (31).
3. Passage through small openings into the central lymph spaces of the villi, aided by intestinal peristalsis or by the contraction and expansion of the villi (17), (22), (1, p. 464).
4. Osmosis and diffusion (1, inferred from (32), (33), (34)).
5. A mechanism similar to that of secreting glands; an inverted glandular process (35).
6. Ingestion by wandering leucocytes or lymphocytes³ (36), (37), (38). A mechanical uptake of substances (26).
7. Physiological activity of the epithelial cells of the intestine (39), (56), or this factor combined with osmosis and diffusion (43).
8. Physiological activity of the epithelial cells combined with a power of the capillary wall to inhibit the passage of diffusible, dissolved sub-

³ For further literature on this subject see Heidenhain (5).

stances from the blood into the gut. The first factor is entirely free of osmotic influences, while the latter may be affected by this force (47), (48), (49), (50).

9. A purely physical process, involving intra-intestinal pressure, molecular imbibition, capillary imbibition, and a power of the blood to "suck" fluid out of the tissues (14).

10. A motor process of the epithelial intestinal cells (40), (41). Filtration by the force of intra-intestinal pressure (42).

11. Dependent upon the solubility of the dissolved substances in lipoids for their passage into the cells, if insoluble in lipoids the path is by the intercellular route (67), (68), (69), (70), (29), (88), (89).

12. Absorbed in accordance with the power of dissolved substances to lower surface tension. This property is also involved in the inhibition of the passage of blood constituents into the gut. Chemical and physical forces may modify this process (83), (84).

13. Determined by the mechanical affinity of the colloid of the intestinal wall for the fluid and dissolved substances, and the swelling or shrinking of the colloid caused thereby. Swelling promotes the absorptive process, while shrinking inhibits it (77), (78), (79), (80).

14. Negative osmosis (91), (92), (93). Cataphoretic electrical fluid current, dependent upon unequal permeability of the intestinal wall for ions, or polarization of the membrane (97), (98), (101).

15. Substances, absorbed by osmosis, are changed within the intestinal wall to non-diffusible products which can exert a further osmotic attraction upon the absorption of other constituents in the intestine (98), (102).

THEORIES OF THE MECHANISM OF INTESTINAL ABSORPTION FOUNDED UPON EXPERIMENTAL INVESTIGATIONS

The intensive application of experimental methods to the study of intestinal absorption began with the work of Heidenhain (43) and his pupils, Leubuscher (44), Gumilewski (45) and Röhman (46). For a number of years previous to the work of these investigators the prevailing idea had been that the theories of endosmosis, first definitely stated by Dutrochet in 1826, adequately explained the process. Experimental evidence for this view is not to be found. It appears quite probable that the early acceptance of the theory that osmosis is responsible for the action of saline cathartics, strengthened the general impression that it is also involved in the absorptive mechanism. As early as 1844

Poiseuille (32) and also Liebig (1848) (33) stated, on the basis of experiments in vitro, that the explanation of the action of cathartic salts is to be found in their osmotic behavior.

In 1869 Voit and Bauer (42) obtained results which led them to conclude that osmosis is not the cause of intestinal absorption. They inclined to the view that filtration brought about by intra-intestinal pressure is the responsible agent. The experimental investigations were concerned with the absorption of protein solutions, serum and salts. The deductions were based partly upon the entirely erroneous premise that the passage of the solutions through the intestinal wall should, if osmosis is an active factor, simulate the diffusion of the same solutions through membranes. The fact that animal membranes may vary in their permeability was, at this time, not known.

Hoppe-Seyler (1881) (39) was the first to maintain definitely that intestinal absorption is a function of the living epithelial cells. The evidence was purely deductive and was, for the most part, based upon the action of the gut in cholera and when poisoned by certain toxic substances. In these instances there is a failure of the normal absorptive function, hence Hoppe-Seyler believes that the "vital" activity of the intestinal cells has been damaged. This type of evidence has been adduced by later investigators, hence it may be well to question its value. Is it not conceivable that delicate colloidal membranes, "vital" or non-living, could be equally affected or, at any rate, show markedly altered permeability due to such radical changes in their environment?

Heidenhain (43), from his own excellent studies and those of the workers in his laboratory (44), (45), (46), was led partially to the same conclusion as that expressed by Hoppe-Seyler. Heidenhain concedes that a certain portion of the fluid and dissolved substance is absorbed from the intestine by osmosis. Another portion does not obey these laws, but is absorbed by the physiological activity of the living epithelial cells. Heidenhain (43) explains his position by stating that when he speaks of the "activity of the living cell" he means thereby only that the cell can exert an influence upon its physical or chemical processes. This investigator insists that he stands absolutely upon the grounds of a purely physical conception of the mechanism.

The experimental findings which led Heidenhain to decide that absorption is partially a function of the living cells of the intestine were as follows: First, because serum of the same and even greater concentration than the blood of the experimental animal, when introduced into the gut, is always concentrated, never diluted, as is evidenced by the

content of total solids. Proteins make up the main portion of the unabsorbed residue. Therefore, there is a direct relation between the absorption of salts and water and the factor causing the concentration, for the Δ of the remaining fluid does not rise. Second, since there is an uptake of fluid from a sodium chloride solution of greater osmotic pressure (measured by the depression of the freezing point, Δ) than the blood. At a concentration of 2 per cent there is finally reached a point where the osmotic power overcomes the physiological absorptive activity of the epithelial cells and, as a result, fluid passes into the gut from the blood. Third, for the reason that chlorides pass out of a solution of 0.3 per cent sodium chloride in the intestine; in other words, there is a passage of solute from a lower toward a higher osmotic pressure, which was contrary to the accepted laws of the behavior of such solutions.

These results enabled Heidenhain to formulate a conception of the intestinal mechanism which combined both the cellular and the osmotic activity. That is, from a sodium chloride solution of higher osmotic pressure than that of the blood the salt is absorbed by osmosis; on the other hand, the water is taken up by a physiological cell activity. Likewise, from concentrations of sodium chloride with a Δ below the level of that of the blood, water is absorbed by osmosis and the salt by the active cellular force.

The effect of small amounts of sodium fluoride, added to the solutions placed into the intestine, seemed to offer a proof of the above statements. When this salt is added to high concentrations of sodium chloride (1.05 to 1.5 per cent), which have a Δ above blood level, there is a decreased water absorption, and only to a slighter extent a decreased uptake of chlorides. On the contrary, sodium fluoride affects the absorption of fluid from sodium chloride solutions (0.3 to 0.4 per cent) of lower Δ than that of the blood less than it does the passage of chlorides. The sodium fluoride, then, a cell poison, inhibits the physiological activity to a greater extent than it does the physical force which is associated with the process.

Cohnheim (47), (48), (49), (50) designed a series of experiments to test whether or not soluble blood constituents can pass into the intestinal contents, with a view of obtaining a measure of the extent to which this occurrence plays a part in adjusting the osmotic equilibrium between the intestinal fluid and the blood. These investigations led Cohnheim to the decision that, under normal conditions, appreciable amounts of diffusible blood constituents do not pass into the intestine. The absorption process is, then, a purely one-way mechanism.

Intestinal absorption, according to Cohnheim, involves two factors: first, an impermeability to body fluids and dissolved substances; second, an ability of the enteric wall to take up the contents from its lumen. The first process is due to the activity of the capillary endothelium, and it is through the intermediation of this structure that osmotic equilibrium between intestinal solutions and the blood is attained without the passage of blood constituents into the gut solutions. The last statement might be interpreted as inferring that osmotic forces are active through the capillary endothelium, although this is not definitely asserted. The second portion of the absorptive phenomenon is a function of the intestinal epithelial cells; it is absolutely free of physical influences. This hypothesis, therefore, differs from that of Heidenhain in that it does not admit that the cellular activity of the epithelium may be affected by the osmotic pressure of the intestinal solutions.

The experimental basis for the above conclusions will be outlined briefly. Working with dogs with Vella fistulas of the small intestine, Cohnheim (47) states that solutions of glucose of all concentrations come into osmotic equilibrium with the blood. This equilibrium, according to the author, is accomplished by the absorption of water or glucose, not by the passage of sodium chloride or other diffusible constituents, from the blood into the gut. It is asserted that the amount of sodium chloride which passes into glucose solutions is small, regardless of whether the solutions are isotonic, hypertonic or hypotonic. When, on the other hand, sodium fluoride (also potassium arsenate) which Heidenhain believed damaged the cell activity of the epithelium is added to a glucose solution in the intestine, Cohnheim (48) observes that the sodium chloride which diffuses into the glucose solution is increased above the amount normally found, under similar conditions, in the absence of the fluoride. There is an increased diffusion between the intestine and the blood vessel contents. In addition, while usually both hypertonic and hypotonic solutions come into an osmotic equilibrium with the blood, in the experiments in which sodium fluoride is added, the concentration of glucose sinks below the isotonic level. Hence, the normal specific ability of the intestinal wall, to allow a passage in but one direction, is lost when poisoned with sodium fluoride. Cohnheim believes that the fluoride has a predilection for the capillary endothelium, although it may also injure the epithelium. Therefore the findings are consistent with the theory that normally the capillary walls possess the power to inhibit the passage of fluid and dissolved substances from the blood.

The one-way absorptive mechanism finds confirmation, also, in experiments in which Cohnheim (49) studied the behavior of sugar solutions in the isolated intestine of cats, rabbits and dogs. Under these conditions the investigator states that he can demonstrate a transport of fluid from the intestinal lumen into the outer surrounding fluid. This conclusion is drawn on the basis of measurements of the gut contents and the weight of the intestine before and after the experiment. As the latter does not show an increase, and since there is a deficit of fluid within the lumen, it is held that there must have been an actual transport.

The absorption stream is, moreover, always in the direction of the outer fluid regardless of the concentration and chemical character of the solutions employed. In short, Cohnheim decides that in this isolated system the fluid stream is not dependent upon the anatomical arrangement of the vessels in the intestinal wall, the mechanical pressure of the musculature, of differences of osmotic pressure, or of solution tension on the two sides of the epithelium, but solely upon the integrity of the intestinal wall which possesses the function of carrying fluid in but one direction.

Rhorer (51) has repeated Cohnheim's experiments on the isolated intestine, using a similar technic, and states that it was not possible in his work to demonstrate a fluid transport.

Waymouth-Reid (6), (7), (8), (9), (52), (53), (54), (55), (56), on the same general grounds as Heidenhain and Cohnheim, decides that the intestinal process is due to the physiological activity of the intestinal cells. Reid states, however, that by the use of the expression "cell action" he does not imply that the forms of energy utilized in the cell mechanism are other than those known in the physical world. This investigator believes that whatever effect physical forces may exert, whether they be osmotic or in the nature of "chemical excitation," their relation is to the cell and not to the blood. If the writer interprets Reid's (56) statements correctly, his theory of the intestinal mechanism assigns the absorptive power exclusively to cellular activity to a much greater degree than did Heidenhain, who conceded that a certain portion of the process is osmotic. Reid stands, perhaps, in closer harmony with Cohnheim, who denies that the intestinal cells are under any physical influences, but does convey a suspicion that the blood vessels of the intestines, which are concerned in holding back blood salts, may be amenable to osmotic effects.

The evidence on which Reid's conclusions are based may be stated briefly. There is an absorption of serum from the intestine of an animal under conditions in which filtration, osmosis and adsorption are excluded (8). Voit and Bauer (42) and Heidenhain (43) had previously noted that serum may be absorbed from the intestine of experimental animals. Furthermore, injury to, or removal of, the intestinal epithelium stops this absorptive process (7) in spite of the fact, according to this author, that such procedures should favor the action of the purely physical forces of filtration, osmosis and adsorption. Indeed, this experimenter finds that any condition depressing the activity of the cells tends to reduce the absorptive action. Previous to Cohnheim and in agreement with him, Reid (52) demonstrated, by means of a diffusion apparatus, using an isolated surviving piece of intestine as a membrane, that transport takes place from the mucosa to the fluid in contact with the muscular coat on the opposite side. In this arrangement, in which osmotic pressure influences may be excluded, simply by placing fluids of the same composition on the two sides of the membrane, it is argued that, since transport occurs, the active force must be a "vital" process inherent in the epithelial cells. Reid (55) repeated Cohnheim's experiments, using an isolated intestinal loop, and obtained results confirming the finding of that investigator, namely, that in such a system there is a fluid transport in one direction only. The reverse process of passage into the intestinal lumen is stated to be the result of cellular injury only, in which case the cells lose their "orienting action." That the osmotic pressure of the blood is not involved in the mechanism of intestinal absorption, Reid (56) believes to have demonstrated by increasing the salt content of the circulating fluid by intravenous injection of sodium chloride and determining its effect upon the uptake of glucose solutions in the gut lumen. Such experiments showed that the degree of water passage from the intestinal fluid is never increased under conditions of increased osmotic attraction of the blood, although in most instances there is a diminished glucose absorption. In addition, no extra chlorides, above the normal amount, are found in the gut content in these experiments. Hence it is concluded that the uptake of water from a solution in the gut, with uninjured epithelium, is not a simple function of osmotic pressure of the sodium chloride of the blood. Since this is the chief blood salt, Reid concludes that it is not probable that any other blood constituent possesses the property of influencing fluid absorption from the intestine.

The work of the three authors detailed above constitutes the chief basis for the theory that the "physiological activity" of the intestinal

cells is responsible for absorption in that organ. Let us now examine the evidence pointing to a physical explanation of the mechanism.

Hamburger (14), (15), (16), (57), (58), (59), (60) does not accept the theory that the process is due to "vital" cell activity, but from his experiments he is led to postulate a purely mechanical explanation of the intestinal absorptive mechanism. This investigator does not deny that physiological or pathological changes can affect the physical forces involved, but he maintains that they do not cease to be purely mechanical (14).

The scheme of absorption from the gut, according to Hamburger (14), (15), (16), is as follows: The epithelial cells take up fluid and dissolved substances by molecular imbibition. This solution makes its way by capillary imbibition through the connective tissue mucosa and is carried away, in small part, by the lymph. The greater portion passes by molecular imbibition into the cement substance of the capillary endothelium or is taken up by the cell itself to go by capillary imbibition into the blood vessels, whence it passes into the blood stream. A tissue has a limited power to imbibe, hence this process would come to an end if the fluid were not taken away rapidly.

Therefore, for transporting fluid out into the capillaries there are, besides imbibition, two other factors. First, there is a power which "sucks" or "sweeps" fluid out of the tissue spaces into the capillary blood stream; this action increases with the speed of the blood flow. Second, intra-intestinal pressure is of importance in the process. In the living animal this pressure may be increased by breathing, by peristalsis and by the weight of the intestines.

Hamburger (14), (15), (16) established the influence of intra-intestinal pressure upon absorption of isotonic sodium chloride solutions in the gut by a series of experiments in which hydrostatic pressure is altered, but the intestine is prevented from expanding by a mechanical device, thus ruling out the factor of an increased exposed surface as the responsible factor in the results obtained. A second method consisted of varying the intra-intestinal force by an alteration of the intra-abdominal pressure and then examining its effect upon the absorption of isotonic sodium chloride solutions. By such experimental methods Hamburger finds that increased intra-intestinal pressure facilitates absorption, as does also a greater intra-abdominal pressure under favorable conditions. When intra-intestinal pressure is reduced to zero or to a slightly negative value the result is a complete arrest of absorption. A positive intestinal pressure of 0.5 cm. still allows of a slow uptake.

Hence, Hamburger believes that the intra-intestinal pressure which will allow of absorption is lower than that in the intestinal capillaries, how much lower it may be depends upon the force of the process of imbibition and the "sucking" action of the blood. In his mechanical theory Hamburger also includes the "suction" and pressure action of the villi, as well as forces of osmosis and filtration (16, p. 191).

Leubuscher (61) had previously performed experiments to test the effect of increased hydrostatic pressure upon intestinal uptake. He found that absorption increased with increasing pressure up to a certain optimum point (80 to 140 mm. Hg). The increase is ascribed, in these experiments, to a simple unfolding and expansion of the surface of the gut. The decrease which follows this optimum point is due, according to Leubuscher, to the effect of the increased pressure upon the blood flow.

Whether or not filtration is active in the transfer of fluid and dissolved substances through the intestinal wall resolves itself, obviously, into a question of whether the intra-intestinal pressure is greater than that on the opposite side of the filter, which is, ultimately, the capillary blood pressure. Reid (8), (9), (55) and also Starling (62), (63) maintain that filtration is not to be considered, since the capillary blood pressure is higher than the intra-intestinal. The former investigator and also Cohnheim (49) have observed that absorption may occur under conditions in which mechanical pressure influences are excluded. Hamburger (14), (16) states that absorption may take place when the intestinal is below the capillary pressure, but believes that at this point the contributory forces of imbibition, "suction of the blood stream," villus movement and osmosis are also at work. The controversy is not settled but, aside from the normal existence of conditions apparently unfavorable for filtration, Hamburger's findings must be tentatively accepted as indicating that variations in intra-intestinal pressure can affect absorption.

Hamburger (59), (60) studied the power of isolated intestinal epithelia to imbibe and to swell when subjected to salt solutions of different concentration. In these experiments support is found for his imbibition theory, for the volume of intestinal cells, and at times even the dimensions of the nucleus may be altered. This seemed to warrant the deduction that the body of an isolated cell is very permeable to sodium chloride, while the nucleus possesses little or no permeability for the salt. It is also demonstrated that the permeability may vary, depending upon the salt and the "state of the cell."

The remainder of the evidence upon which Hamburger bases his theory deals with the behavior of salt solutions toward structureless, homogeneous membranes (agar, gelatine and collodion), isolated tissues used as membranes, and also the diffusion phenomena in the intestines of dead dogs. In the experiments employing dead, isolated intestinal and other tissue as a diffusion membrane, Hamburger (58) believes to have demonstrated perfectly the "one-way diffusion" of the intact intestine. Hence this demonstration, states the author, is not in agreement with Cohnheim's idea that the intestine possesses a "vital" factor simply because of its property of passing a fluid stream in one direction. On the whole, the experimenter concludes that the difference between "dead" and "living" membranes is merely quantitative. Artificial membranes were constructed with which Hamburger (57), (58) was able to duplicate all the phenomena exhibited in the intestinal absorption of sodium chloride solutions and even of serum. All of these factors, then, led him to the conviction that enteric absorption is brought about by a purely physical or mechanical process.

Höber (64), (65), (66), (67), (68), (69), (70) performed experiments designed to compare the rates of diffusion of a series of salts with their speed of absorption in the intestine. The results of the investigations led him to conclude that physical forces are involved in the mechanism, even though they do not fully explain the process, and though the speed of absorption is not strictly comparable to the membrane behavior of the solutes tested. Further studies convinced him that salts are absorbed into the intestinal cells only if they are lipid soluble, in agreement with Overton's idea that lipid solubility determines cell permeability. On this basis Höber points out that the intestinal epithelium behaves toward dissolved substances like other cells, that their plasma membrane acts like other protoplasm, and does not require a special power of uptake, as was usually supposed. The dissolved substances which have a parallel rate of intestinal absorption and speed of diffusion are lipid insoluble and pass between the cells. Other materials, which have a greater speed of absorption than of diffusion, are lipid soluble and pass through the cells. This theory, the author states, is not inconsistent or conflicting with any osmotic explanation of the process.

In order to explain how this mechanism affects the absorption of salts and other bodies, it is set forth that all inorganic salts and sugars with six or more carbon atoms, in general all lipid insoluble substances, pass between the cells. Iron is the one discovered exception in regard to this rule for, although it is not soluble in lipoids, it passes into the

cells. Lipoid soluble materials, as urea, glycerine and ethyl alcohol, are taken into the cells through their surfaces.

The relation of speed of absorption in the intestine to lipoid solubility is borne out in the work of Höber's student, Katzenellenbogen (71). Heidenhain (5) had previously decided that the intercellular cement substance of the villus epithelium is open for at least part of the absorbed materials.

Wallace and Cushny (72), (73) independently and at about the same time as Höber (64), published experiments in which they compared the rates of absorption of a large number of equi-molecular salt solutions with that of a 1 per cent solution of sodium chloride. Their results, however, do not agree with those of Höber in showing a parallelism between the rates of absorption and of diffusion. They find that readily dissociated salts, whose ions possess a great speed, are not always absorbed faster than less dissociated salts with weaker ionic speed. Wallace and Cushny (73) affirm that these facts do not necessarily indicate that the intestinal cells operate only by a "vital" activity, but it is more likely that the absorptive process is due to a chemical relation of colloid to salts, of such a nature that the cell may take up one salt easily and reject another.

The observations of Höber (64) and Wallace and Cushny, that various salt solutions of the same osmotic pressure have a different speed of absorption, due to an unequal rate of passage of their ions, are of great importance. They showed clearly that the intestinal wall does not possess an equal permeability to all dissolved substances. Further one cannot expect to get a strict comparison of rate of diffusion through membranes and intestinal absorption. We are dealing, then, with a membrane of varying permeability, depending upon the nature of the salt presented to it. A lack of appreciation of this fact led many workers to erroneous conclusions before this time.

Goldschmidt and Dayton (74) performed experiments, using colonic loops of dogs, which led them to the conviction that osmotic processes are active in the mechanism of intestinal absorption. Toward solutions of sodium chloride the colon acts essentially like a permeable membrane. On the other hand, solutions of sodium and magnesium sulphate behave in the colon as though they were separated by a semipermeable membrane. It is also demonstrated that the absorptive process is related to the salt content and osmotic concentration of the blood. In addition, the osmotic pressure exerted by the gut contents, which in turn is dependent upon the permeability of the intestinal membrane

for the solute, are factors in inhibiting the passage of blood constituents into the gut contents. The osmotic pressure and the permeability of the enteric wall for the solutes in contact with it also determine the speed of passage into the blood of other dissolved substances simultaneously present in the gut without evidence of injury to the intestinal mechanism. Goldschmidt and Binger (75) showed that the permeability of the intestinal wall may be altered, that is, increased or diminished, without demonstrable evidence of physiological injury. In other words, the intestinal membrane may exhibit a changing permeability, dependent upon the chemical character and the concentration, within physiological limits, of salts in contact with it. This conception also includes the possibility of one solute affecting the passage of another either by altering its state in solution or in a manner which is dependent upon their relative power to pass through the membrane.

DIFFUSION THROUGH THE INTESTINE OF DEAD DOGS

Whether the non-living intestinal wall behaves similarly to that of the living animal has been a subject of much controversy in deciding whether or not the mechanism of enteric absorption involves the integrity of the living cell. Hamburger (14), (15) found that absorption of sodium chloride solutions and of horse serum proceeds in the intestine of dogs, dead from 1 to 24 hours, in the same order as from living animals. This supports the investigator's theory that the process is purely physical. It will be remembered that Hamburger (57), (58) has also claimed to have duplicated the process of intestinal absorption, in some of its apparently non-physical details, with structureless homogeneous membranes.

Cohnheim (47), (50) criticises Hamburger's experiments on dead animals on the grounds that, since the blood is stagnant in the vessels, there is so little fluid on the blood side that qualitatively the same results would be obtained as in the living animal. The agreement, therefore, he states is only apparent. To imitate more closely the normal process Cohnheim perfused the abdominal vessels by inserting a cannula into the inferior vena cava after the death of the animal. Nevertheless, with this procedure, an animal taken directly after death behaves toward solutions in the intestine like the intact animal. The conclusion is drawn that the epithelium is not dead, therefore the experimenter destroyed it with heat (hot water at 80 to 90°C.). After this treatment it is found that sodium chloride of the vascular perfusion fluid passes into a glucose solution in the gut in accordance with a purely diffusion

process. If the vessels are not perfused Cohnheim confirms the results obtained by Hamburger; that is, a behavior similar to that in the living animal. Cohnheim further states that in an animal dead for some time (5 hours) there is very little absorption with or without destroying the cells by heat.

Höber (66) attacks the experiments of Cohnheim, quite justly, by questioning whether treating the epithelium with heat leaves an intestine which differs from that of the living animal only in the lack of living active epithelial cells. The former performed experiments in which he determines that, when the intestine of a dead dog is treated with heat according to Cohnheim's method, it does not act toward solutions in the same manner as the untreated intestine of similar dogs, even in the absence of perfusion. He argues that if the intestine of a dog which has been dead for 24 hours does not behave like a physical membrane, then it ought not to do so even though its vessels are perfused. The discrepancy is explained as due to pressure differences. Cohnheim attempted to maintain the perfused sodium chloride under normal pressure, but Höber points out that the normal opposing pressure is absent, namely, that due to contraction of the intestinal, diaphragmatic and abdominal musculature. The latter further states that there is only a quantitative difference between the absorption from the intestine of a dead and a living dog. This, he asserts, is due not only to a failure of the pressure factors mentioned above, but also to the absence of the "sucking" action of the blood stream. Further, the only discrepancy between diffusion and absorption is that diffusion through membranes behaves the same in either direction, while absorption carries dissolved substances in a special direction.

Goldschmidt and Dayton (74) carried out a few experiments upon the changes of volume and composition of distilled water and of sodium chloride solutions in the colon of dead animals. The fluid absorption is practically nil, as is also the exchange of dissolved substances.

PHYSICO-CHEMICAL FACTORS POSSIBLY INVOLVED IN THE ABSORPTIVE
MECHANISM, FOR THE MOST PART BASED UPON
THEORETICAL CONSIDERATIONS

In addition to the theories of the absorptive mechanism of the intestine, based upon experimental evidence, there are many in the literature in which from analogy physico-chemical principles are applied as explanations of the phenomenon. In this class may be included the process of imbibition, first applied to absorption through the blood

vessels by Magendie (68) and later (31) suggested by him as possibly associated with intestinal absorption. Magendie thought of the villi as "soft sponges" which imbibed fluids.

The modern investigations on this subject are due principally to the researches of Hofmeister (77) which deal with the uptake by colloids of solvents and solutes from a long list of salt solutions, together with the capacity of the latter to produce swelling or shrinking of the colloids. These data led to the formulation of the "Hofmeister series." Hofmeister has suggested that this phenomenon of mechanical affinity for water and solute, with the attending change in volume of the colloidal substance, may play a rôle in the body and especially in intestinal absorption. If such be the case, he continues, one need not assume that the process is of a "vital" nature. It has previously been pointed out in this paper that Hamburger believed that molecular and capillary imbibition were an essential part of his physical theory.

Pauli (78), although he points out that the cells represent a more complicated system, believes that he can reconcile Hofmeister's results on the swelling of gelatine with Heidenhain's findings on intestinal absorption.

Fischer (79) advances the prediction that the laws governing colloidal imbibition will do more to give an insight into the phenomenon of absorption than the laws of osmotic pressure and diffusion have done.

Bechhold (80) asserts that the belief that osmotic forces were involved has been a hindrance to progress in this field of investigation, and that only a recognition of swelling and shrinking of colloids as dominant factors can furnish a satisfactory explanation of the mechanism. He further states that salts which, as a rule, promote uptake of water in the intestine, also favor the swelling of fibrin and gelatine. Bechhold expands upon the subject, stating that electrolytes which cause shrinking may impede not only their own absorption, but that of other salts, while substances rapidly diffusible and favoring swelling act contrariwise. The cathartic salts, according to Hofmeister's classification, belong to the group of electrolytes which hinder swelling, hence if the above statement is true they should impede the diffusion of other salts. Results quite out of harmony with this hypothesis were obtained by Goldschmidt and Dayton (74) who found that sodium sulphate, instead of hindering, markedly speeds the diffusion rate of sodium chloride in the colon.

Mayerhofer and Pribram (81) present experiments to show that the permeability of isolated sections of the intestines of rabbits and guinea-

pigs is partially a function of their water content. The more water the intestine contains, the more permeable it is for water solutions. By imbibition or desiccation a membrane can be made artificially more or less permeable. They believe, moreover, that by water withdrawal a condition akin to that characteristic of acute and chronic intestinal diseases may be produced. Quagliariello (82) reports that he was unable to distinguish any difference in the power of isolated intestinal tissue of dogs to take up sodium chloride and sodium sulphate.

The rôle of capillarity and surface tension in intestinal absorption is not a new problem, but it has received further attention in recent times. Traube (83), (84), on purely theoretical grounds, believes that surface tension plays an important part in the mechanism. He has found that of all the substances which Overton studied plasmolytically, the greater the speed with which it passes into the cell, the greater is its power to lower surface tension. It is this investigator's idea that surface tension is the driving force or cause of osmosis. To the combined factors he gives the name "Haftdruck" or "adhesion pressure." The more the surface tension of a solvent is increased or diminished by a dissolved substance, the greater or less is the "adhesion pressure" of the solute. Therefore, the osmosis of a solute is more rapid the smaller its "adhesion pressure." Intestinal absorption, according to Traube, may be influenced by this factor in the following manner. The uptake of fats, for instance, is aided by the power of bile to lower surface tension. Also, the question why sugars go directly into the blood, while fat is absorbed by the lymph stream, is associated with surface phenomena. However, these influences are subject to alteration by other factors. That is, even though the lymph has a lower surface tension than the blood, the nature of the pressure in the capillaries may carry substances in that direction. Further, chemical activity and above all the composition of the membrane may modify the mechanism. If, for instance, the membrane contains fatty particles, then the surface tension of fluids passing through it decreases and thereby modifies the speed of passage greatly. If a membrane on one side contains lipoids and on the other not, it can happen that the surface pressure may be altered by the lipoid content, and the direction of the diffusion stream is altered or even reversed. In other words, the "adhesion pressure" on opposite sides of a membrane is an all-important factor in determining the direction of the fluid passage; hence the writer postulates a cause of the failure of blood constituents to pass into the intestine. Furthermore, he states, one need not wonder that

serum or plasma may be absorbed, as was found by Voit and Bauer, Heidenhain, and Reid, for the amount of lipoid on the mucosa surface of the gut makes its surface tension less than on the opposite side. This theory, Traube states, does not include the solubility of substances in lipoids in the sense of Overton, but only the influence which undissolved lipoid may exert upon surface tension.

Török (85) and Buglia (86) put the theories of Traube to an experimental test, adding to solutions (sodium chloride or peptone) subjected to intestinal absorption substances (bile, bile salts, gum arabic, etc.) which lower surface tension. The results, they say, are not in agreement with Traube's views. In no case was an increased absorption demonstrated. It has long been known that bile is essential for the absorption of the products of fat digestion, and it is of interest to note that as early as 1852 Bidder and Schmidt (87) suggest that this action is associated with the effect of bile upon capillarity.

It may be well to review briefly the theory of Friedenthal (29), (88), (89) which meets with the approval of Munk (90). Friedenthal, after a full consideration of the subject, decides that the processes of osmosis and filtration suffice qualitatively to explain the absorption from the intestine of soluble constituents. For water-insoluble substances, however, he maintains that there is a type of affinity of the material for the cell protoplasm, depending upon its solubility in the components of the cell structure. This conception, on the whole, is very similar to that of Overton and of Höber. Friedenthal emphasizes the point that water and protoplasmic solubility are totally different. This then would explain how water-insoluble substances such as fats, soaps, etc., may be absorbed.

It is evident that absorption from the intestine may take place against an osmotic pressure gradient. Otherwise stated, there is a passage of a fluid stream from a place of higher to one of lower osmotic pressure, a negative osmosis. Furthermore, isotonic solutions of diffusible salts may be absorbed. Both of these facts have in the past been difficult to explain, but they have now found their counterpart in purely physico-chemical systems. Dutrochet (1826) recognized that negative osmosis may occur under certain conditions. He found that acids offer a mode of action opposed to that of alkalis, namely, with an alkaline solution the current of endosmosis directed itself from water toward the solution, while with acid the current flowed toward the water.

Lazarus-Barlow (91), (92) has demonstrated in membrane experiments that the initial rates of osmosis of glucose, sodium chloride and

urea in equimolecular solutions are not the same as exist between their final osmotic pressures or freezing point differences. The nature of the membrane, and even the effect of albumen in solution, may alter the initial rate of osmosis. As an illustration, with a peritoneal membrane osmosis can occur between isotonic solutions, or there may be an osmotic flow from a solution having a higher toward a solution having a lower final osmotic pressure. Barlow (92) calculates that, from the initial rates of osmosis, a physiological saline is really of a concentration of 1.6 per cent. Therefore, according to his observations, if osmosis is an occurrence in the organism, one would expect to get a passage from hypertonic solutions of diffusible salts. Moore, Roaf and Webster (93) also arrive at the conclusion that substances in physiological systems will always pass against an osmotic pressure gradient, not because of the membrane impermeability, but for the reason that the cell colloids possess an affinity for crystalloids.

Negative osmosis or, in fact, an osmotic stream in any direction, may be related to a presence of electric potential in that direction, or electro-osmosis. Engelmann (94) and others have shown that the secretory activity of glands is accompanied by electromotor phenomena, while Rosenthal (95) discovered an ingoing electrical current in the stomach mucosa of frogs and rabbits. Reid (9), (96) considered and tested the occurrence of electrical potential changes during absorption through frog's skin and rejects the idea that it has any relation to the process, for he finds that both secreting and absorbing membranes have an electrical stream in the same direction. In addition, Reid was unable to increase the rapidity of fluid transfer from the outer to the inner surfaces of frog's skin by connecting a conductor on the two sides and arranging the current so that the amount flowing in the skin against the direction of absorption was reduced. This worker further maintains that in order that the electrical stream be effective, there must be a greater "porosity" in one direction.

Höber (97) and Oker-Blom (98) believe that an absorbing membrane is the seat of electro-motor activity, which may be an effective mechanism in the absorptive process. The electrical current has its source in any difference of potential on the two sides of the colloidal membrane. Such a state can be established by an unequal diffusion of electropositive or negative ions. If, for instance, a membrane is permeable to positive ions of an electrolyte and relatively impermeable for the negative ions, then there will exist a great degree of electrical potential difference between the two sides. This condition results in a cataphoretic

electrical diffusion stream in the direction of the current flow. It is thus apparent how even the direction of a diffusion flow may be altered by these influences.

Höber (97) takes up Reid's objections to electro-osmosis as a factor in absorption and believes that they can be satisfactorily met by the conceptions just outlined.

Girard (99), (100), (101) has applied his ideas of electro-osmosis to the absorptive process in the intestine (101). It is his belief that, in the case of electrolytes at least, osmosis is essentially electrostatic, and the presence of hydrogen or hydroxyl ions may alter the process. He states that in order to explain the results obtained by Heidenhain and others, it is only necessary to assume that there is in contact with the membrane a liquid with ions active from the point of view of electrification of contact (as conceived by Perrin). These ions are adsorbed by the membrane and change its sign. If, now, the liquid on the opposite side of the membrane possess the reverse charge, there is a difference of potential sufficient to polarize the membrane, resulting in a force determining the passage and direction of the osmotic stream. We have in these researches, tentative explanations of the negative osmosis and absorption of isotonic solutions from the intestinal tract.

Oker-Blom (98), (102), after a critical survey of the subject, accepts osmosis as a qualitative explanation of the mechanism of intestinal absorption. In addition, he formulates a hypothesis in which the substances absorbed—in some instances by conversion into non-diffusible products—can exert their osmotic attraction upon the absorption of other constituents in the intestine. Thus, a solution of apparently higher osmotic pressure than the blood may be absorbed. Starling (103) strongly favors the view that the cells of the intestine actively intervene in the process of absorption. However, he states that the osmotic pressure of the non-diffusible colloids of the blood may exert an osmotic attraction sufficient to account for the uptake of isotonic solutions from the gut.

CRITIQUE OF THE FOREGOING INVESTIGATIONS

The experimental work bearing upon the subject at hand has been presented above and the hypotheses arising therefrom are set down. The reader of this résumé, therefore, has before him a basis for formulating his own judgment of the relative merits of these different views. However, it is not outside the task of a reviewer to take upon himself this function. Hence an attempt will be made to present a short,

critical analysis of the subject of the mechanism of intestinal absorption based upon a full consideration of the experimental work and suggested theories.

In this presentation it is assumed that absorption from the entire length of the intestinal tract involves a similar mechanism. A review of the investigations designed to test, or incidentally bearing upon, the absorption of fluids and dissolved substances at various points of the small intestine and the colon, justifies the conclusion that the differences are quantitative rather than qualitative (104 to 114, inc.).

At the start it may be pointed out that a few facts have found confirmation by many observers, namely:

1. Water and certain dissolved substances, in the intestine, are absorbed from hypertonic solutions—as indicated by the Δ . Under such conditions the solute is absorbed in concentrated solution. The more closely the Δ of the intestinal contents approaches that of the blood, the greater is the concentration of the absorbed solute, while the fluid passage rapidly decreases.

2. Solutions of a sufficient degree of hypertonicity draw fluid into the gut.

3. Both solvent and solute pass from hypotonic solutions.

- a. Below about 0.6 per cent concentration of sodium chloride in the intestine the salt is absorbed in very dilute solution; water passes more quickly than the solute.

- b. At a concentration of sodium chloride of approximately 0.6 per cent, or at a point in close agreement with the blood content of this salt, the solvent and the solute are absorbed at the same rate. Therefore the strength of the intestinal fluid suffers little change.

4. Salt solutions, capable of exerting an osmotic pressure, but which are not, or to but a slight extent absorbed (i.e., sodium or magnesium sulphate), come into osmotic equilibrium with the blood, regardless of their initial concentration. The non-diffusible salt makes up the total osmotic pressure of the intestinal solution.

- a. It is stated repeatedly in the literature that, similarly, glucose solutions of all concentrations come into osmotic equilibrium with the blood. The writer believes that this statement must be made with reservation, since the evidence that glucose alone exerts the osmotic pressure in the gut under such conditions, is not entirely consistent.

5. Blood constituents pass into the intestinal contents in but small amount under ordinary conditions.

There are other observations touching upon this question of the intestinal absorptive mechanism, which are either in dispute or their rôle is undetermined. These may be stated in the form of interrogations, as follows:

1. Does the blood in its composition, distribution, or by the physical forces which it exerts as a fluid stream, have an influence upon the absorptive process? Is the mechanism purely local?

2. Is the intestinal wall a strictly irreciprocal membrane; that is, do dissolved materials pass in but one direction?

- a. Is the fluid which passes into hypertonic solutions of the saline cathartics, or other salts, a secretion, a true osmotic fluid flow, or the result of an injury to the intestinal epithelium?

- b. Are the blood constituents found in the intestinal test solutions, secretions of the cells? Can the osmotic concentration of the gut fluids exert an influence upon the passage of these substances, or may they also be the result of an injury to the intestinal mucosa?

3. Is intra-intestinal pressure a factor in the absorptive process?

4. Does the intestinal wall present the properties of other colloidal protoplasmic membranes?

- a. May its permeability be altered, aside from the production of an injury to the cells?

5. Do the solubility relations between the intestinal wall and the substance in contact with it play a rôle in absorption?

6. Are the factors of imbibition, surface tension and electro-osmosis active agents in the intestinal mechanism?

7. Is the process purely physical or entirely a function of the living intestinal epithelial cells, or a combination of both?

The first question has already been partially discussed in the introduction above, and evidence presented which indicates that alterations in the amount of blood flowing through the intestinal vessels, in a unit of time, can affect the rate of absorption in the normal organism. It is of interest in this connection that Marriott (115) has found that in certain types of marasmus, the so-called *athrepsia*, there is a diminished blood volume with a concomitant decrease in volume flow (116) of the circulating fluid. These conditions are suggested as a causative agent in the impairment of the absorptive function of the gastro-intestinal tract in this disease.

Although Reid (6), (7), (8), (9) admits the facts just stated, he (56) and (less emphatically) Cohnheim (48), (49), do not concede that the osmotic pressure of the blood may influence the absorptive process.

Reid bases this conviction upon his failure to get an increased fluid absorption from glucose solutions in the gut, when the sodium chloride concentration of the blood is raised by infusion. On the other hand, he observed in these experiments that there is a decreased sugar absorption. These results, so far as they go, have been confirmed by Goldschmidt and Dayton (74). D'Errico (117) has also reported that in whatever fashion the molecular concentration of the blood is altered, that is, increased or diminished, tap water introduced directly into the intestine is immediately absorbed, and in either case there is a lowering of the molecular concentration and electrical conductivity of the blood serum. Starling (103), (62) states the proposition thus: "But in every case absorption by the alimentary surface is a question of the local conditions rather than of the needs of the organism as a whole." In explanation he proceeds to say that only in extreme cases of hydraemic plethora can the process of intestinal absorption be influenced, never in the normal animal. This is undoubtedly true, if it is meant thereby that in a normal organism all the products of digestion are absorbed as they are presented to the intestinal mucosa. The need of the body for a particular product is probably not a determining factor. We know, also, that the intestine does not discriminate in passing into the blood substances which may or cannot be assimilated by the body (118).

These limitations granted, it must be pointed out that there is evidence that the molecular composition of the blood must exert some influence upon absorption from the gut, both in the normal and abnormal state. First, as has been indicated above, it has been repeatedly shown that certain solutions in the intestine, whether hypertonic or hypotonic, come into osmotic equilibrium with the blood. It may be tentatively stated that this is a law of intestinal absorption. Furthermore, sodium chloride solutions, in isolated loops, adjust themselves in a partial pressure equilibrium with the chlorides of the blood (74). Goldschmidt and Dayton (74) have shown that increase of blood chlorides, either spontaneously or by infusion, affects this equilibrium level. It cannot alter our case to say that the intestinal cell is the intermediary factor, for the fact remains that the blood is the ultimate cause. It would seem, then, that the *milieu* of the organism is not to be considered entirely passive in this process.

It is certain that under normal experimental conditions large amounts of blood constituents do not pass into fluids in the intestine. It is of importance to consider this point for it involves fundamentally the

question whether osmosis is a consideration and whether the intestine is a strictly one-way membrane. That chlorides, carbonates and some nitrogenous bodies, if only in small amount, do pass into the intestine is evidenced by the findings of many investigators. Gumilewski (45) considered that the chlorides which he found in distilled water in the gut represented a secretion from the cells. Reid, on the other hand, maintains that the passage of chlorides into the intestine under such experimental conditions is the result of an injury by the distilled water. Goldschmidt and Dayton (74) found that chlorides pass into distilled water in the colon in amounts which have been considered to be the normal cellular secretion by previous investigators. However, they observed that when the concentration of chlorides reached a certain point (0.16 per cent) a re-absorption began. Physiologically there is no evidence of injury; the colon behaves toward sodium chloride solutions, after having been exposed to distilled water, as before. If the distilled water is repeatedly removed large amounts of chlorides may be withdrawn from the organism in this manner. If this phenomenon is to be ascribed to cell secretion it is an interesting fact that the absorptive power of the intestine serves to keep the mass of the secreted chlorides at a fixed low level. Goldschmidt and Dayton further show that the point at which re-absorption surpasses the passage of chlorides into distilled water in the gut is raised when the chloride content of the blood is increased by infusion. It may be argued, also, that the extra chlorides found in this instance merely represent a secretion greater than the normal amount. D'Errico (117) states that intravascular injection of hypertonic sodium chloride causes a secretion of the intestinal tract of higher molecular concentration than the normal secretion. However, he notes that introduction of water hinders the secretion and that absorption is also reduced for a time.

There is still another link in the evidence: Goldschmidt and Dayton noted that when sodium chloride solutions of a concentration of 0.6 to 1.0 per cent are placed in the colon, the solute rapidly adjusts itself to an equilibrium with the blood chlorides. But the Δ of the solution is greater than can be accounted for by the chloride content alone. All the facts, which cannot be discussed here, point to the passage of other substances from the blood into the intestinal solution at this time, in an attempt to adjust the total osmotic pressure of the fluid in the intestine to that of the blood. Diena (119) has observed precisely the same behavior, and has identified some of the blood constituents present. Priestly (120) found that when large amounts of water are

drunk by man the electrical conductivity of the blood serum is diminished. He ascribes this occurrence to a passage of blood salts into the intestinal contents. Several investigators have noted increased salt output in the feces accompanying catharsis (121), (122), (123). Frey (124), (125) arrives at the conviction, on excellent evidence, that the chlorides found in glucose solutions in the small intestine owe their presence to an osmotic equilibrium adjustment between the blood and the intestinal contents. He finds that more chlorides pass into hypotonic than into hypertonic solutions of glucose in the gut. This investigator believes that the presence of a cell injury is excluded in his experiments. Frey and also Cobet (126) find that the upper and lower portions of the small intestine differ in their capacity to "secrete" chlorides as well as to absorb solutions.

It may be added in passing that Goldschmidt and Dayton (74) believe that the diffusion of blood constituents into intestinal solutions is a function of the osmotic pressure of the gut contents, and is also dependent upon whether or not this osmotic pressure is due to diffusible or non-diffusible substances. An isotonic solution of a non-diffusible salt (i.e., sodium sulphate) permanently inhibits the passage of chlorides from the blood into the colon. If the sulphate injured the colon cells, according to Reid, more chlorides should be found in the fluid than normally. If secretion of the cells were responsible for the chlorides in intestinal fluids under other conditions, we should expect to find the so-called "normal amount" here also; such is not the case. In view of the evidence presented, the conclusion is warranted that the intestinal membrane is not irreciprocal but may allow salts to pass in either direction.

It would scarcely seem necessary to discuss whether the statement just made also applies to fluids. It is a universal experimental finding that hypertonic solutions of sufficient concentration call forth a liquid stream into intestinal loops of experimental animals (126 to 134, inc.). The larger number of these experiments deal with the mechanism of the action of cathartic salts, but for the purpose of this discussion we shall deal only with the general problem. The point at issue is whether this fluid stream represents an active secretion, a pure osmotic flow, or whether it is the result of an injury.

Goldschmidt and Dayton (74) noted that diffusion of fluid from the blood does not begin until the concentration of sodium chloride in the colon is above 1.2 per cent. If the osmotic pressure of the blood is increased by sodium chloride infusion the concentration of chlorides in

the gut, which is necessary to draw fluid from the body, is still higher than normally. Hay (128, p. 243) found that if means were taken to limit the intake of water in an animal, administration of sodium sulphate results in a failure of catharsis. Furthermore, this observer (128, p. 391) determined that saline purgation with strong solutions causes a blood concentration. It would appear, therefore, that the fluid stream into the gut bears a definite relation to the relative osmotic pressures of the gut contents and the blood. In addition there is no doubt that the source of the fluid is the blood. These facts are *prima facie* evidence that we are dealing with a true osmotic flow.

Further proof of the nature of this process is found in the work of Brodie (135), (136) and his collaborators. Their experiments have shown that there is an increased oxygen consumption and blood flow, above that of the normal resting state, in the small intestine when sodium chloride, distilled water and Witte's peptone are absorbed. On the other hand, when hypertonic magnesium sulphate is present in the intestine, such increase of oxygen consumption does not occur. The statement is made that this result would appear to favor the view that the transport of water into the magnesium sulphate is due to physico-chemical causes rather than to active secretion.

It will be noted that in Brodie's experiments distilled water caused an increased oxygen consumption, while hypertonic magnesium sulphate did not. It has been alleged that both injure the intestine. If so, from these results we must assume that the injuries are of a different nature. Many observers have claimed that strongly hypertonic solutions of salts, especially the saline cathartics, cause changes in the intestinal mucosa (137), (138), (139). Heidenhain (43) states that there must be a limit to the concentration of salt which the epithelial elements of the intestine will stand without injury. Nevertheless, he admits (140) that the secretion caused by hypertonic salt solutions in colon loops is due to an endosmotic capillary transudate and not to a glandular secretion. Furthermore, the colon glandular cells exhibit no anatomical alterations from such an osmotic stream.

If the intestinal wall possesses some of the properties of a diffusion membrane—and such a conclusion seems warranted—it might be expected to exhibit the variabilities of behavior which are so characteristic of colloidal systems. It is well known that protoplasmic colloids are in a markedly delicate state of equilibrium, which is especially sensitive to and altered by electrolytes and the presence of hydroxyl and hydrogen ions. This being the case, it is not difficult to understand that

the permeability of colloidal membranes may be easily affected by changes in their environment. The result is evidenced by an increased, decreased, or total change in the membrane behavior.

In a colloidal system, moreover, surface tension phenomena are very active and may indeed be the cause of the changes mentioned in the preceding paragraph. Therefore, the possibility of such factors exerting an influence in the mechanism must be considered.

Aside from surface actions the character of the diffusion process may be altered by differences of electrolyte environment on the two sides of the membrane. The charge conferred by such a state upon opposite surfaces of a membrane is of importance in the mechanism of electro-osmosis and electrical cataphoresis. This phenomenon is especially capable of demonstration in the intestine, but must be accompanied by a more exact knowledge of the relative speed of the passage of ions and molecules through the gut wall.

That the speed of diffusion of substances may be altered in the enteric tract has been mentioned above in regard to solutions of mixtures of sodium sulphate and sodium chloride. Goldschmidt and Binger (75) have noted that when increasing amounts of calcium lactate are added to a constant concentration of sodium chloride, the diffusion rate of the latter salt is first increased and then diminished. A consideration of the experimental findings in their investigation led Goldschmidt and Binger to the opinion that the effect is due to changes in membrane permeability.

Analogies to this action can be found in the literature. Cohnheim (48) observed that quinine retards water absorption from solutions in the intestine. Reid (9), (56) noted that the presence of sodium chloride in glucose solution favored the uptake of the glucose from the gut, which action he designates as a "chemical excitation." Many observers have noted that the presence of one salt may affect the absorption of another in the intestine (141 to 144, inc.). It is interesting that apparently sodium chloride facilitates the intestinal absorption of proteins, peptones and gelatine (42), (145), (146). There is, in addition, an isolated observation which indicates that the permeability of the gut may be influenced from the side of the blood. Fisher and Moore (147) find that in many experimental conditions in which sugar appears in the urine, none is demonstrable in the enteric tract. However, if sodium chloride is injected intravenously during the hyperglycemia, sugar is excreted into the small intestine. This action is attributed to an alteration in the permeability of the intestinal mucous membrane.

It is evident that the intestinal mechanism is not wholly irresponsive to physico-chemical forces the exact nature of which are, to be sure, obscure, but which are supposedly associated with its colloidal structure.

To conclude, in answer to the last question formulated above, it must be apparent, from the evidence presented, that the mechanism of intestinal absorption is qualitatively explained by the known laws of osmosis. The researches of Traube, Girard, Perrin and others demonstrate that the van't Hoff theory of osmotic pressure is inadequate to explain all the phenomena which may be attributed to osmosis. Physico-chemical investigations planned upon this basis are now bringing to light new facts which show a closer agreement between purely physical systems and body membranes. It would seem that eventually the information thus obtained will be of great aid in elucidating such questions as the one under discussion in this paper. In this connection Loeb (148) has recently obtained results of inestimable value. He shows that the diffusion of water through a membrane is dependent for its direction and rate of migration upon a charge conferred upon the water molecules by the membrane. This, in turn, is a function of the chemical nature of the membrane as well as of the valency, the concentration, and the sign of the charge of the ions in contact with it.

Of the many investigators who have considered the subject, Hoppe-Seyler, Reid, and perhaps Cohnheim, have alone insisted upon a purely "vital" interpretation. That factors other than osmotic may be active in modifying the process has been indicated. All the evidence points to their physico-chemical nature, and much useful research may still be expended before one need seek refuge in that last resort, "vital cell activity."

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**AN ANALYSIS OF SOME OF THE FACTORS OF
VARIABILITY IN THE VITAL CAPACITY
MEASUREMENTS OF CHILDREN**

**D. J. EDWARDS
AND
MAY G. WILSON
NEW YORK**

AN ANALYSIS OF SOME OF THE FACTORS OF VARIABILITY IN THE VITAL CAPACITY MEASUREMENTS OF CHILDREN *

D. J. EDWARDS AND MAY · G. WILSON
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The use of vital capacity measurements of the lungs in a comparative way implies a certain standard of reliability of the measurements on the normal subject. If the observations made on the normals cover a wide range of variability, then small differences, such as may well arise from moderate disturbances in function, will be obscured, and the practical value of the test greatly diminished.

In adults the limitations and practical usefulness of vital capacity measurements have been clearly shown in the work of Peabody,¹ West² and others. More recently, we have applied the test to children and have indicated a line of usefulness in this field.³ A question concerning the reliability of the results naturally arises, however, when vital capacity measurements are made on young subjects, since there are two outstanding ways in which the test, as applied to children, may be expected to yield more variable results than when applied to adults. First, the satisfactory performance of the test depends in large measure on an immediate and complete forcing-out of the air from the lungs when the test is made, and young subjects present some difficulty in getting a thorough expulsion of the air; and second, it is necessary to relate vital capacity to some other body measurement, such as height, weight, or body surface area, and during the growing period these body measurements are subject to marked change and individual differences.

The present study is an attempt to determine to what extent different methods of measuring the vital capacity influence the final values, and to define in a statistical way the amount of variability exhibited in a large series of vital capacity observations on children who were selected only with respect to the age limits of from 6 to 16 years and to clinically normal subjects.

Methods of Measuring the Vital Capacity.—In a previous paper³ dealing with the vital capacity of children with heart disease we have given a figure representing the mean value obtained on a group of

* From the Departments of Physiology and Pediatrics, Cornell University Medical College.

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normal subjects. While this work was in print, Emerson and Green⁴ reported observations on the vital capacity of normal children of about the same age range that are significantly lower than those obtained by us. We have, therefore, studied the matter further in an attempt to discover some of the reasons for the apparent difference in the two sets of observations. Our observations were made with a specially constructed spirometer of the Gad-Krogh type. In the calibration of this instrument the water displacement method was first used to measure off the liter divisions, and then the entire scale was checked against a ten liter Bohr meter. A recalibration of the instrument has recently been made and this was found to confirm the original values. We believe, therefore, that errors in calibration can be excluded as a possible cause for the higher values obtained by us.

A second method of checking our results has been to compare the readings obtained with our instrument with those obtained on the same subjects with other spirometers. Thirty-six subjects, ranging in size from 0.83 to 1.54 sq. m. surface area, were selected for the first series in the test. The measurements of the vital capacity were taken on each subject with three spirometers and with only a few minutes intervening between each set of observations. The instruments used beside our own were the Sanborn, made by the Sanborn Company, of Boston, and the Standard, made by the Narragansett Machine Company, of Providence. The Standard instrument was calibrated by the same method as that described above and a corrected scale placed upon it.

The Sanborn instrument gave results that agree very closely with those obtained with our instrument. The average figure for the series shows a difference of a little less than 1.5 per cent., with the Krogh instrument giving the higher values. When the results are arranged into groups on the basis of the surface area of the subjects there is shown a remarkable parallelism of the values obtained with these instruments throughout the size range. With the Standard spirometer the results show consistently lower readings amounting to a difference of a little more than 10 per cent. for the averages of the group, when compared with the figure obtained with our instrument. There is also greater variation from group to group than is exhibited in the results with the other instruments.

In another series of 115 cases we have compared the results obtained with other Standard spirometers (not calibrated by us) with those obtained with the Sanborn. It should be noted, however, that the measurements in this series with the Standard instruments were not taken at the same sitting, but at a previous time ranging from a few

4. Emerson, P. W., and Green, H.: *Am. J. Dis. Child.* **22**:202 (Sept.) 1921.

days to as much as a month. It will not be possible, therefore, to relate these values in a quantitative way. The significant feature in these results is the greater variability in the group averages given from the measurements with the Standard spirometer over those obtained on the same subjects with the Sanborn instrument.

Another series of tests has been made, similar in procedure to the above, to compare the measurements obtained with a Dry spirometer made by Thomas Upham, of Boston, with those obtained with the Sanborn. Forty-one subjects were included in this series, and the average values for the group exhibit lower readings with the Dry spirometer by about 11.6 per cent. We are not justified in placing very much stress on this quantitative difference, since the measurements were not taken on the same date. But observations covering much longer intervals make it evident to us that the lower reading with the Dry spirometer cannot be explained on the basis of time changes.

It is indicated from these results that certain types of spirometers tend to give lower readings than others and that the group values obtained with the low reading spirometers generally exhibit greater variability. Differences of this character result in no small degree, we believe, from the use of instruments not sufficiently sensitive for the measurement of the vital capacity of children.

Another factor that appears to account for part of the discrepancy between the observations reported by Emerson and Green and those we have obtained is in the different method used for estimating the surface area. They employed, for the most part, the Benedict-Talbot method, whereas we have used exclusively the DuBois height-weight method. In order to obtain some notion of the extent of influence which this difference in the method of estimating the surface area might have on the final results, we selected at random ten cases published in the tables by Emerson and Green and have calculated these on the basis of the DuBois surface area chart. The results show an average about 12 per cent. higher than their figures for the same subjects.

These considerations, while indicating two factors which make for the lower vital capacity values reported by Emerson and Green, do not account for the comparatively large difference between their findings and those we have obtained. If more complete data were available concerning technic and character of the subjects, it might suggest other factors that have contributed to the discrepancy, but in the absence of such material it is of no avail to speculate.

Variation of the Vital Capacity in a Group of Normal Subjects.—In a group of thirty-five children in whom stem length, chest circumference, height, weight and vital capacity were taken we found³ that

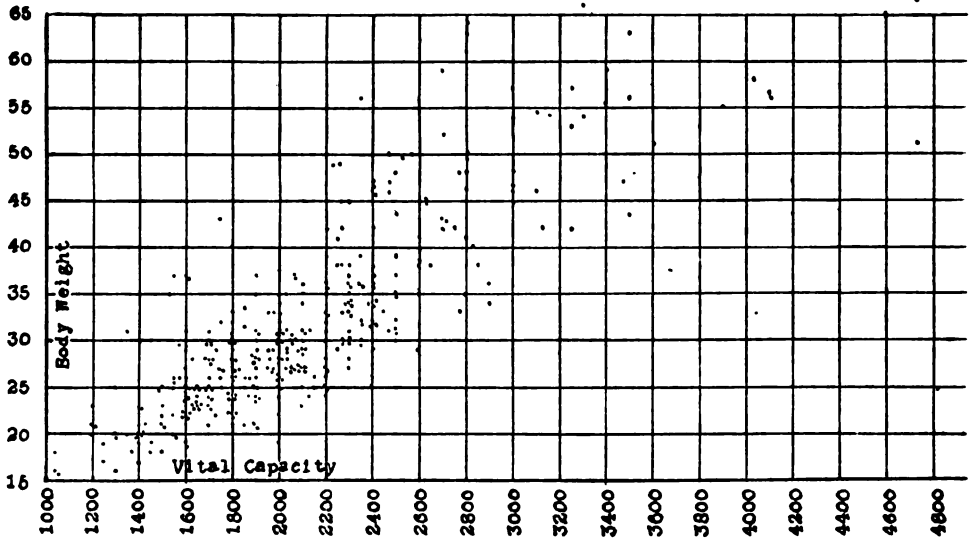


Chart 1.—Body weight (kg.) against vital capacity (c.c.).

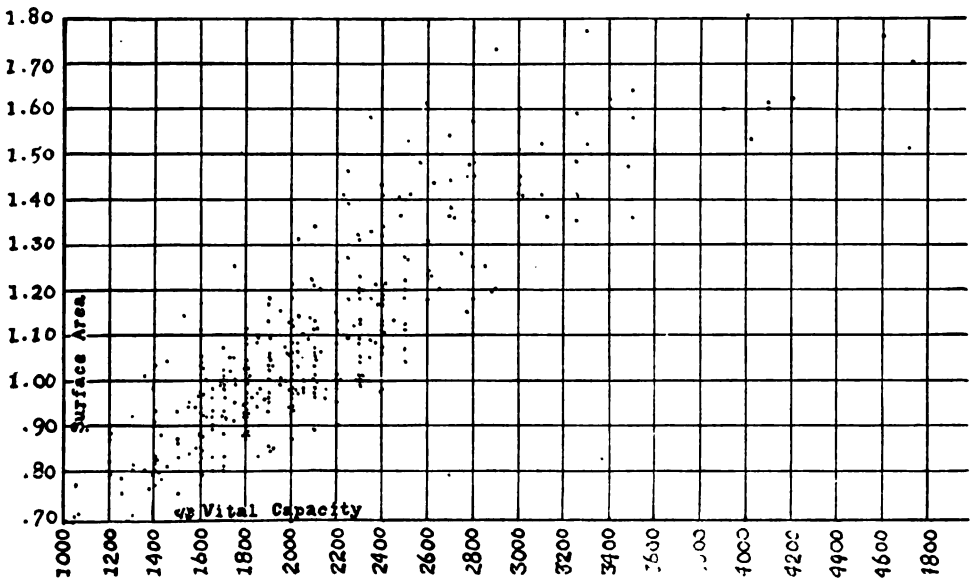


Chart 2.—Surface area (sq. m.) against vital capacity (c.c.).

in using Dreyer's⁵ standards for vital capacity the correlation to the surface area measurement (surface area calculated from the DuBois height-weight chart) appeared to be as close as that to any of the other body measurements. On the basis of this and also the work of West² and of Dreyer⁶ on adults, the surface area unit was adopted for relating all our vital capacity measurements. The work has been extended so that we now have records of the vital capacity, height and weight of 360 clinically normal children. This amount of material has seemed to warrant a closer study of the degree of variation exhibited, with a view to a more exact evaluation of its significance and better methods of expressing the results.

At present there is, in general, no better way of gaining a clear impression of the degree of variability of a series of observations

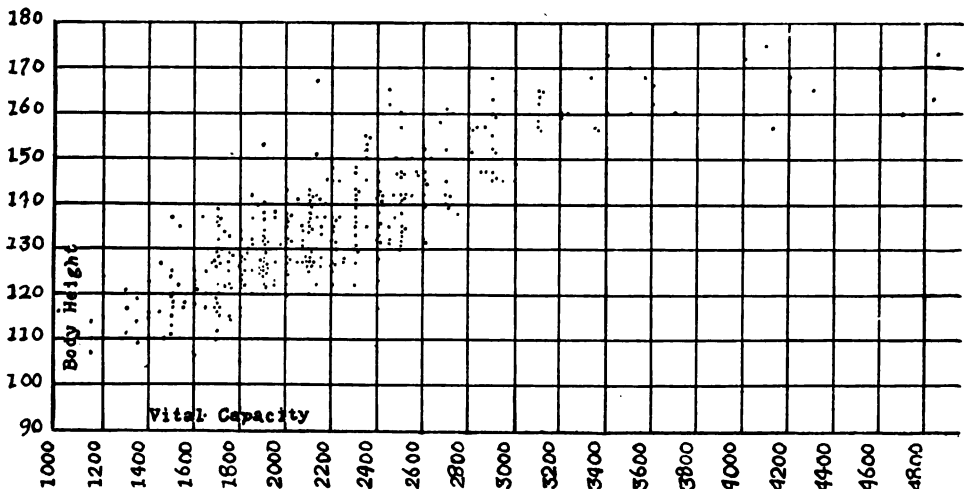


Chart 3.—Body height (cm.) against vital capacity (c.c.).

than to arrange them in the form of a plot. Although somewhat more time consuming, this method has the advantage of showing at a glance in which part of the range of variables there is present the greatest degree of scatter. In the present analysis the data have been arranged to plot the vital capacity as related to weight, to height and to body surface area.

An examination of these plots, shown in Charts 1, 2 and 3, reveals the greatest degree of scatter when the body weight is taken as the

5. Dreyer, G., in collaboration with G. F. Hanson: *The Assessment of Physical Fitness by Correlation of Vital Capacity and Certain Measurements of the Body*, with Tables, Cassell and Company, London, New York, Toronto and Melbourne, 1920.

6. Dreyer, G.: *Lancet* 1:197, 227, 1919.

measure of relationship; also that there is little difference between relating the vital capacity to surface area and that relating it to height alone. In the weight relation the greatest amount of scatter is shown by the measurements taken on the larger subjects. This we interpret to mean that the factors which make for variability in weight are operative to a greater extent in children weighing more than 40 kg.

The plot for the height relation shows a fairly well grouped set of observation throughout the range. The method of relating the vital capacity to surface area presents a close correlation in that part comprising the smaller subjects, but, like the weight relation, shows divergence as we approach the higher vital capacity readings from larger subjects. This feature of the surface area relation naturally follows from relations previously shown for the height alone and for the weight alone, since the method of deriving surface area contains an element of both factors.

In the light of these results, the method of relating the vital capacity to a body height measurement seems indicated as a general practical procedure. This does not imply that the vital capacity measurement in children is more closely correlated to body height than it is to surface area as we have derived the latter, but it is interpreted rather to indicate that the inherent errors in the weight measurement, when deductions have to be made for clothing, and the accumulative errors, when surface area calculations are carried out from these measurements, more than offset the slight difference in absolute correlation which the surface area relation may contain.

In turning now to the problem of the closeness of correlation of the vital capacity to the surface area it will be important to remember that our subjects present a normal group from an ordinary clinical standpoint. Beyond this it is impossible to speak with exactitude in regard to their soundness; in fact, in the light of more recent work, there is reason for believing that a small percentage of the group would reveal abnormal conditions with more exact methods of diagnosis. It is of interest to note, therefore, that the standard deviation of this series, which gives a measure of the variability in terms of the unit in which the variable is measured, i. e., in liters vital capacity per square meter body surface area, is 0.272 for the 360 cases. To obtain a measure in relative terms of the variability of different characteristics measured, it is customary to express them as percentages of their individual means. This coefficient of variation ($C. of V. = \frac{100 \sigma}{\text{mean}}$) in the present series is found to be 14.2 per cent.

In variability, as measured in the absolute terms of the standard deviation and in the derived relative term of the coefficient of variation, our series shows a value slightly greater in magnitude than certain

other physiological measurements, such as the pulse rate and the heat production in adults,⁷ but it is less than that reported on such measurements as keenness of sight⁸ and heat production in infants.⁷

The results of this brief comparison indicate that our series shows a satisfactory agreement with the results of others on fairly comparable physiological measurements. The agreement seems rather remarkable when one considers the probable influence of age, sex, race, the small percentage of cases not strictly normal, and the differences in mental cooperation in the test.

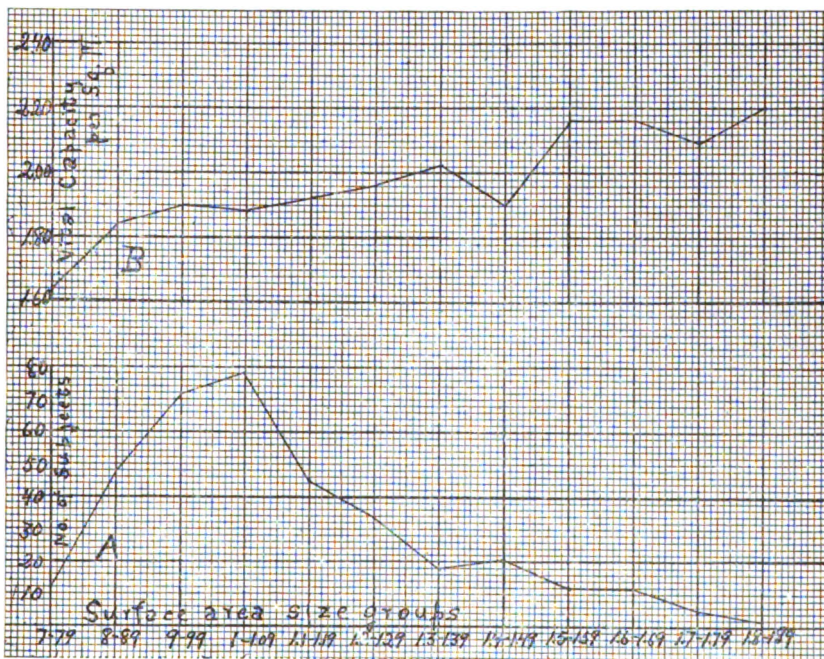


Chart 4.—(A) Distribution of subjects grouped according to surface area size. (B) Average vital capacity of each group in surface area size arrangement.

Vital Capacity as Related to Body Size.—In the course of these observations on the vital capacity of children, as related to surface area, we have been impressed by the frequency with which low readings were obtained on small children, and similarly a tendency for larger subjects to give higher readings.

The surface area measurement, containing as it does a height and weight element, probably expresses more exactly than any other body

7. Harris, J. A., and Benedict, F. G.: Carnegie Institution of Washington, Pub. 279, 1919.

8. Pearson, K.: *The Chances of Death and Other Studies in Evolution*, E. Arnold, London, 1897.

measurement the body size relation of groups of subjects differing markedly in their individual proportions. On the basis of this conception of body size, we have divided the whole range of our 360 cases into groups of convenient units as regards their surface area size. Each subject was then assigned to the appropriate group with his vital capacity calculated on the basis of his surface area. The mean value for each group was then determined with a view of showing to what extent size introduces a variable in a statistical average for the whole series.

The results of this method of analysis are very well brought out in Chart 4. The curve at the bottom (A) shows the frequency distribution in terms of the group totals. It exhibits a skew type of curve with the mode at about 1 sq. m. surface area size. This form of the curve merely signifies that, in selecting our subjects from the ages of six to sixteen, inclusive, we have inadvertently obtained a preponderance of subjects in the lower half of the range. The upper curve (B) of the mean vital capacity for each size group shows a distinctly upward trend from the smaller to the larger sized subjects. The slope of the curve suggests that, with a larger number of cases, it would give a straight line cutting approximately the point 1.74 at the lower, and 2.18 at the higher range. This would give roughly a 25.2 per cent. range, which is probably statistically significant. It indicates that in the evaluation of an individual vital capacity measurement on the basis of surface area some account has to be taken of the actual size of the subject measured before an accurate estimate of the deviation from the normal can be made. It follows, therefore, that a single mean value derived from a large group of widely differing sizes of children offers only an approximation to the true mean of any individual class.

It is of interest in this connection to consider the possible meaning of the type of curve presented by this method of grouping according to body size. There is suggested the operation of at least three factors, either separately or in common: First, the method of deriving surface area may contain an element of inaccuracy with diminishing stature; second, the method of measuring the vital capacity may similarly introduce a constantly increasing error with smaller subjects; and third, the vital capacity in terms of its absolute relation to body size may undergo an increase in children as they approach maturity. The data at hand afford no basis for determining the degree of operation of these different factors.

It is pertinent to this discussion to note that in the grouping of the subjects according to the surface area size there is naturally a certain amount of segregation of age relations. The subjects comprised, for example, in the group from 0.7 to 0.79 sq. m. surface area,

are as a group younger than those included in the group from 1.20 to 1.29 sq. m. An analysis of these group results will show, therefore, whether less variability goes with greater maturity and stature. If we use as a measure of variability the coefficient of variation, it is evident from the accompanying table that the small young subjects do not give values significantly more variable than shown by the older and larger subjects.

THE VARIABILITY OF THE VITAL CAPACITY MEASUREMENTS SHOWN BY DIFFERENT GROUPS ARRANGED ACCORDING TO SURFACE AREA SIZE

Group	No. of Cases	Maximum	Minimum	Percentage Range	Mean	Standard Deviation	Coefficient of Variation
0.7-0.79	12	2.97	1.28	61.8	1.64	0.233	14.2
0.8-0.89	49	2.85	1.37	71.5	1.84	0.252	13.9
0.9-0.99	72	2.44	1.42	71.8	1.90	0.220	11.6
1.0-1.09	79	2.34	1.33	76.0	1.89	0.237	12.5
1.1-1.19	45	2.38	1.33	79.0	1.92	0.232	12.1
1.2-1.29	34	2.30	1.41	68.0	1.96	0.234	11.9
1.3-1.39	18	3.10	1.41	120.0	2.02	0.260	12.9
1.4-1.49	22	2.36	1.54	53.0	1.90	0.208	10.7
1.5-1.59	12	3.23	1.48	118.0	2.18	0.350	16.0
1.6-1.69	12	2.88	1.52	89.5	2.18	0.500	22.9
1.7-1.79	5	2.77	1.57	76.5	2.09	0.248	11.9

These results support the conclusion that the observations made on small young children are statistically as reliable as those obtained from the more mature subjects; moreover, they indicate that the lower mean values shown in the curve of Chart 4 for the subjects of small surface area size are probably not due to an error inherent in the method, which is inversely related to size and age of the subjects measured.

SUMMARY

The measurement of the vital capacity of children with certain types of spirometers has given results 10 per cent. or more below that obtained on the same subjects with other instruments. Moreover, the results obtained with those instruments giving low readings exhibit a greater degree of variability. It is suggested that the low readings of a more fluctuating character are probably due to the use of a spirometer not sufficiently sensitive for the measurement of the vital capacity of children.

The vital capacity observations on 360 normal children, when related separately to the body measurements, height, weight and surface area, exhibit a correlation slightly to the advantage of the height relation. It is suggested that the height unit may be the most practical body measurement for the relating of the vital capacity of children; not that the absolute correlation is greater than the surface area unit, but rather that the chances for errors in the calculations are less and in practice will more than offset any fundamental difference there may be in favor of the surface area method.

The absolute variability in this series, as shown by the standard deviation, is 0.272 liters per square meter surface area. The coefficient of variation is shown to be 14.2 per cent., a value agreeing fairly well with that of other physiological variables of a comparable nature.

Based on the surface area measurement as a criterion of body size, certain groupings have been made. The mean vital capacity of each of these groups was obtained, and from these data it has been shown that the vital capacity, as related to a unit of surface area, exhibits gradually increasing values from the smaller to the larger-sized subjects. This difference is estimated to be of the order of a 25 per cent. range for the size groups.

In terms of the coefficient of variation, the groups comprising the smaller surface area size, which were likewise made up of younger subjects, do not exhibit greater variability than the groups of larger surface area size made up of older subjects. It is argued that the age factor does not make for greater variability in the measurement of the vital capacity of children.

CONCLUSIONS

1. A spirometer that offers minimal resistance to the egress of the air from the lungs is necessary for measuring the vital capacity of children.

2. The correlation between vital capacity and body height is more intimate than that between vital capacity and surface area, or body weight.

3. The vital capacity values obtained from children show a degree of variability about equal to that exhibited by other fairly comparable physiologic variables. Young children give results that are not more variable than those from older ones.

4. Children of small stature exhibit a lower vital capacity per unit of surface area than those of larger stature.

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